LEUKEMIA CUTIS

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LEUKEMIA CUTIS

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With an Introduction by

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INTRODUCTION

In the study of leukemia cutis the dermatologist shares an interest with the internist, the hematologist, the radiologist and the pathologist In the area of diagnosis, however, the role of the dermatologist is pre eminent In many of the patients afflicted with leukemia the cutaneous lesions are the windows through which we may discern the underlying disease and the correct evaluation of these lesions will often lead to an early diagnosis

It is altogether fitting therefore, that a dermatologist has assumed the laborious undertaking of collecting in one monograph the tremendous amount of knowledge that his been recorded about the various aspects of this terrifying group of diseases Dr Bluefarb is eminently qualified for this monumental task His work with a vast number of patients at Bellevue Hospital and Cook County Hospital has enabled him to make many contributions of his own to the literature on leukemia In addition the length and breadth of his experience in this field have given him the mature judgment needed to review and to evaluate nearly one thousand articles on leukemia and to extract from each the material pertinent to this monograph

In these days of increasingly defined departmentalization of the teaching and practice of medicine it is heartening to see so important a contribution to a subject being made not by a [illegible]
by an [illegible]
the t[illegible]
by in[illegible] training are encouraged to make their [illegible]

In producing this beautifully organized monograph, Dr Bluefarb has placed in his debt all who are concerned with the medical practice, teaching or investigation of leukemia For all of us in this field he has made the task much easier for assessing the past and surveying the present For the investigator he has in addition illuminated brightly the road ahead

"Bluefarb on Leukemia Cutis bids well to become an important milestone on the road to progress It is hoped that the author will continue his work on this series of monographs so as to provide us in time with an authoritative source of information for all the cutaneous manifestations of the diseases of the reticuloendothelial system

Marcus R Caro, M D

PREFACE

THIS VOLUME, LEUKEMIA CUTIS, is the third in a series [illegible] on the cutaneous manifestations of reticulo- [illegible] of [illegible] this [illegible] group of diseases In these cases [illegible] es- [illegible] splenomegaly [illegible] blood [illegible] s rather [illegible] primitive elements which are capable of [illegible] lympho cytic monocytic, or granulocytic tissue are present in the skin The ability of such cutaneous diseases as leukemia cutis a reticuloendothelial system disease, to mimic other dermatoses is an interesting facet of this study It may, in this respect be compared to syphilis, which also involves the reticuloendothelial system in its ability to simulate many other *cutaneous entities This factor was aptly described by* Nanta "La morphologie des lesions cutanees est indifferente a la variete des affections hematologique en cause" Definite specific impressions are apparent in a study of leukemia cutis Chronic lymphocytic leukemia appears to occur frequently in men and women during the climacteric The occurrence of acute leukemia in adults has been reported frequently of late, whereas this type of leukemia was formerly found to occur much more *frequently in the first two decades of life* This sudden increase in the acute form of leukemia in adults leads to speculation as to whether the "sulfa drugs or other so-called "wonder" drugs, administered for minor, trivial infections may be causative factors There may also be potential solutions to this problem in determining the reason why ane-

mia, purpura, or other hemorrhagic tendencies and allergies, such as drug reactions, urticaria or asthma, frequently precede the development of leukemia Other factors which warrant investigation in leukemia cutis include whether the development of cutaneous leukemic tumors is due to the awakening activity of hematopoietic sites in the dermis or to a possible infiltration from blood vessels into the skin It should also be determined why cutaneous leukemic tumors occur *more frequently in the so called "aleukemic" phase of* leukemia Why are specific cutaneous lesions more frequent in lymphocytic leukemia than in granulocytic leukemia (an incidence of 10 to one) and why is the face rarely involved in granulocytic leukemia, while in lymphocytic leukemia involvement of the ear lobes, nose and eyebrows often produces disfigurement simulating the leonine facies present in leprosy? The question of pruritus is also unanswered This is a prominent symptom when so called toxic lesions, such as prurigo like papules, are present but seldom occurs with specific lesions such as nodules or tumors

These observations are stated in this monograph with the hope that *investigation, particularly through the study of the* reticuloendothelial system of the skin, will be stimulated Thus the collection of such observations seems to us to warrant the publication of a monograph on leukemia of the skin [illegible] possible, to [illegible] e for Classification of the Nomenclature o[illegible] C[illegible] [illegible]ses of the Blood and Blood Forming Organs In some instances, however, certain "pet terminology appeared to have been used by individual investigators or research groups These designations not listed in the Committee report, we did not attempt *to clarify but have left their specific interpretation to the* reader *While reviewing a fairly voluminous literature for this* series of monographs we were often dismayed by the inconsistency of the descriptive designations Many reports which were possibly of significance were discarded because any interpretation of them would have been mere assumption It

it not surprising that such great confusion exists regarding these leukemic states

One minor phase of this confusion concerns the descriptions of the cutaneous manifestations The majority of dermatologists appear to be extremely imaginative and their choice of phrases to describe the size and color of these lesions is unlimited Our dermatologic literature is to say the least extremely colorful although not very scientific in this respect

The most comprehensive review of these descriptive designations used in dermatology was presented by Bernard Appel M D (Decadent descriptions in dermatology *Arch Dermat & Syph* 62 370 (Sept) 1950) Among the many amusing—and confusing—descriptions which he cited was that of the frequently used "hemp seed" size He stated It was not possible to obtain hemp seed because it is from a narcotic plant (cannabis marijuana) and cannot be legally possessed without a special federal license A lesion described to be the size of a hemp seed must therefore remain somewhat of a mystery unless recourse is had to an encyclopedia" Appel suggested that the size of a lesion be designated by units of measure such as millimeter or centimeter

We have consulted and quoted freely from all the publications on this subject which are included in the bibliography We wish to acknowledge our indebtedness to these contributors and to their publishers We are indebted to Irving Fried man M D Associate Director Hematology Division Hektoen Institute Cook County Hospital together with Stanley Leithold M D for contributing the excellent chapter on the hematologist s approach to leukemia Our sincere thanks is also due to Marcus R Caro M D for reading this manuscript and writing the Introduction to this volume We are most grateful to Arthur Curtis M D Herbert Rattner M D and Steven O Schwartz M D for their kindness in reading these manuscripts and for their very valuable suggestions We wish to thank Maurice J Costello M D and William A Ford M D for permitting the use of their illustrations We are also much indebted to Miss Sophie Price of the Medical Library Staff

Northwestern University Medical School, for verifying the bibliography and to Miss Madge Walsh, Chief Medical Photographer, Northwestern University Medical School, for preparing the photomicrographs We also wish to extend our sincere gratitude to the members of the staff of Charles C Thomas, Publisher, for their constant assistance and cooperation Were it not for their efficiency, it would not have been possible to present a series of this type within such a comparatively short period of time Finally, I wish to express my sincere thanks to my wife, Grace Parsons Bluefarb, for her constant encouragement, as well as for her practical assistance with the numerous details of editing typing and proof reading during the past 15 years

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LEUKEMIA CUTIS

I

INTRODUCTION

LEUKEMIA is a disease in which there is a proliferation of immature tissue cells rather than of white blood cells These immature cells are apparently derived from the reticuloendothelial system The blood picture may or may not reflect what is occurring in the tissues, hence, the paradoxical designation of some cases as "aleukemic" leukemia The histologic findings in various organs of the body are similar, regardless of whether the peripheral blood reflects a leukemic or an "aleukemic" picture

Leukemia is usually classified according to either the duration of the process or to the type of cell which predominates in the peripheral blood or bone marrow In the acute forms, the cells are often so immature that it is impossible to identify their origin whether from granulocytic lymphocytic or monocytic cells The most immature type of cell is the so called stem or blast cell Such cases of acute leukemia are designated as "stem cell or "blast cell" leukemia

The incidence of leukemia is reported to have increased from one per 100 000 population in 1900 to 4 3 at the present time It has been estimated that there are 15 000 to 20 000 cases of leukemia in this country at all times, with about 5 000 new cases and 10 000 deaths from leukemia each year (see table)

The following table lists the number of deaths and the mortality rates in the United States for the years 1952 1953 and 1954 (695)

transmission of the spontaneous disease, follows definite genetic laws This receives additional support from two clinical sources One is that the occurrence of two or more cases in one family cannot be explained on the basis of chance alone, according to Sturgis (662b), and the other is the demonstration by Videbaek (698a) that the incidence of the condition in blood relatives of patients having leukemia is 17 times as great as in comparable control groups The disease has also been considered to be congenital in origin F Miller (450a) reviewed the literature and described a case of congenital leukemia in a boy This infant, the third child of healthy parents, died 20 minutes after birth from a bilateral tentorial fissure with intracranial hemorrhage There was evidence of tumorous (leukemic) cutaneous infiltration and the diagnosis was congenital leukemia In the literature, Miller found 13 definitely proved cases of congenital leukemia, nine probable cases of congenital leukemia, 21 cases in which leukemia was present at a very early age but intrauterine origin could not be ascertained and 10 cases in which the diagnosis appeared to be in some doubt although they were reported as "congenital" leukemia Based on this study, Miller concluded that granulocytic leukemia (usually postnatally acute with considerable numbers of myeloblasts and "paramyeloblasts" appeared to be the predominating type in congenital or very "early occurring leukemias and it occurred more frequently in boys and men than in girls and women

There are obviously many factors concerned in the statistical increase in the frequency of leukemia, especially of the acute type Poor diet and possibly the prolonged ingestion of adulterated or contaminated foods may play a part in some cases according to Leonard and Wilkinson (380b) It has long been recognized that the incidence of leukemia in radiologists and dermatologists is significantly higher than the occurrence of this disease in physicians who are not repeatedly exposed to roentgen rays A recent report by March (425) dealt with this subject He showed, in a study covering a 20 year period that this disease occurs nine times more often in

SIXTH REVISION OF THE INTERNATIONAL LISTS

Year	1952		1953		1954	
	Total Deaths	*Mortality Rate*	*Total Deaths*	*Mortality Rate*	*Total Deaths*	*Mortality Rate*
All Causes	1,496,838	961 0	1,517,541	958 5	1,481,091	918 9
Neoplasms						
Neoplasms of Lymphatic and Hematopoietic Tissues						
Leukemia and "Aleukemia"	9,841	6 3	9,918	6 3	10,440	6 5
Lymphocytic Leukemia	4,073	2 6	4,035	2 5	4,180	2 6
Granulocytic Leukemia	3,021	1 9	3,003	1 9	3,324	2 1
Monocytic Leukemia	648	0 4	644	0 4	723	0 4
Acute Leukemia, Type Not Specified	884	0 6	977	0 6	987	0 6
Other and Unspecified Leukemia	1 215	0 8	1,259	0 8	1,229	0 8

In 1954 the total death rate of 918 9 deaths per 100,000 population was the lowest ever recorded for the United States However, there was an increase in the number of deaths from leukemia in that year

Etiology

The etiology of leukemia is still an unsolved problem which has stimulated much study and speculation Leukemia resembles malignant neoplasms in many ways and it has come to be regarded by most investigators as essentially a neo plastic process Recent work, on the other hand, has em phasized the possibility that a living (viral) agent may be concerned These views, indeed, are not irreconcilable nor mutually exclusive

It has been demonstrated in animals, especially in rats and mice, that the susceptibility to experimental leukemia, and the

onset of the disease and there had been an acute cutaneous reaction on at least one occasion He presented diffuse cutaneous atrophy and radiodermatitis of the entire neck and alopecia of the entire scalp Several keratoses and small cutaneous carcinomas had appeared which had been treated with electrosurgery or by excision During the following years he continued to receive treatment for the psoriasis and several more cutaneous carcinomas appeared which were also removed He finally manifested universal redness and thickening of the skin which improved slowly following treatment However, approximately one year later he died from acute granulocytic leukemia The occurrence of acute granulocytic leukemia following prolonged iodine-131 therapy for metastatic carcinoma of the thyroid gland was reported by Seidlin *et al* (620) They described two patients with acute leukemia in a series of 16 patients who had metatastic carcinoma of the thyroid gland All had been treated with prolonged irradiation, solely from an internally administered radioisotope

Pochin *et al* (760) reported a patient in whom acute leukemia occurred 18 to 24 months after the administration of a total dose of 7 1 mc radioactive iodine (I^{131}) for hyper thyroidism After calculating the radiation doses provided to various sites of the body, they concluded that the development of leukemia was probably only coincidental However, the following year, Werner and Quimby (761) observed another patient in whom acute leukemia occurred following similar therapy They stated that this "reopens the question whether such an association may not be more than chance" Their patient, a 28 year old woman, had received 2 1 mc of radioactive iodine (I^{131}) for hyperthyroidism Acute granulocytic leukemia was present 18 months after this therapy According to Werner and Quimby, five patients (an incidence of one per 13 000 per year) were found to have acute leukemia following this treatment but "Mechanisms by which the relatively low radiation exposures provided by I^{131} therapy in hyperthyroidism might induce leukemia are not evident The conclusion that the association of leukemia and I^{131} therapy is

physicians who are exposed to irradiation He emphasized that the occupational hazard of roentgenology has not been given sufficient attention and that the standard means of protection are inadequate and difficult to employ in routine work. It is also of interest in this connection that, in a study of 5,000 Japanese at Hiroshima and a small number at Nagasaki, Bugher (83) found that in persons who had received effects from the atom bomb, leukemia occurred 10 to 20 times more frequently than in persons who were not exposed to this radiation Furthermore, those who were directly under the atom bomb blast, where exposure was greatest, were most prone to leukemia Lange *et al* (369) reported 75 established cases of leukemia among atomic bomb survivors in Hiroshima and Nagasaki up to December 31, 1952 There were 38 men and 37 women in this series and the leukemogenic effects of radiation were manifested equally in both sexes and at all age levels Among 76,891 survivors who, at the time of the bombing, were at a distance of less than 2,500 m from the point on the ground immediately below the bomb burst (hypocenter), there were 65 cases of leukemia Among 159,285 survivors who were beyond 2,500 m, there were only 10 cases of leukemia These data indicate a great increase in the incidence of leukemia among atomic bomb survivors due to a single massive exposure to ionizing radiation Among the 75 patients with leukemia, 31 (41 per cent) had chronic granulocytic leukemia, 20 (26 per cent) had acute granulocytic leukemia and only one had chronic lymphocytic leukemia The preponderance of chronic granulocytic leukemia, as compared with chronic lymphocytic leukemia, is striking However, it is pointed out that chronic lymphocytic leukemia is comparatively rare among the Japanese Although leukemia is still occurring in atomic bomb survivors, there has been a steady decline in these cases since 1950

F. W Lynch (409b) presented a 53 year old man who had extensive cutaneous lesions of psoriasis which had been present for 35 years He had received a considerable amount of roentgenotherapy during a period of 25 years following the

onset of the disease and there had been an acute cutaneous reaction on at least one occasion He presented diffuse cutaneous atrophy and radiodermatitis of the entire neck and alopecia of the entire scalp Several keratoses and small cutaneous carcinomas had appeared which had been treated with electrosurgery or by excision During the following years he continued to receive treatment for the psoriasis and several more cutaneous carcinomas appeared which were also removed He finally manifested universal redness and thickening of the skin which improved slowly following treatment However, approximately one year later he died from acute granulocytic leukemia The occurrence of acute granulocytic leukemia following prolonged iodine-131 therapy for metastatic carcinoma of the thyroid gland was reported by Seidlin *et al* (620) They described two patients with acute leukemia in a series of 16 patients who had metastatic carcinoma of the thyroid gland All had been treated with prolonged irradiation, solely from an internally administered radioisotope

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no more than a chance one is supported by the results of 10 years' experience"

The use of P^{32} therapy for polycythemia vera was reviewed by S O Schwartz and Ehrlich (615d) They found reports of 30 patients who had both leukemia and polycythemia vera Among these, 25 had previously received irradiation therapy for the polycythemia vera It was their opinion that in patients with polycythemia vera and leukemia, the leukemia occurs as a result of previous irradiation therapy

It was stated by Dameshek and Gunz (139g) that "of the various etiologic factors proposed for leukemia in human beings, the only one that appears to be rather conclusively established is that of ionizing radiation The evidence for this includes (a) the incidence of leukemia in radiologists which *is 8 to 10 times as great as that in physicians in other fields,* (b) the incidence of leukemia in those surviving the atomic blasts near the hypocenters of Hiroshima and Nagasaki, which is 12 times as great as that in survivors at the periphery of the blasted areas, (c) the relatively high incidence of leukemia in individuals in Britain and Holland treated for spondylitis by x-rays, (d) the development of leukemia in individuals treated for enlarged thymus by x ray, and (e) the possible leukemogenic effects on the baby of the taking a roentgenogram of the pregnant woman's abdomen to determine fetal size and position In addition there are the numerous experiments in animals, including those showing the leukemogenic effects of x-rays and nuclear radiation

Other stimulating factors which have been incriminated are "sulfa" drugs, sunlight, hormonal imbalance, tars, benzols, gasoline fumes, phenols, chrysarobin and other cutaneous irritants, according to Leonard and Wilkinson (380b)

The infectious etiology for leukemia was probably one of the first to be considered since leukemia occurring in fowls was shown to be due to a virus Because many infections of bacterial origin cause hyperplasia and immaturity of the cells of the bone marrow, it was easy to suppose that other infections would cause maturation arrest at more immature or

leukemic levels However, no bacterium, virus, fungus, protozoan, spirochete or rickettsial body which will cause leukemia has been demonstrated and many investigators have administered human leukemic cells and leukemic bone marrow, by all conceivable routes, to human beings without transmission of the disease Gross (246) reported the results of very convincing experiments on the role of viruses in animal leukemia and A Kirschbaum (342) showed that the virus is harbored by the leukemic cells and causes an illness which hastens death from leukemia However, he did not consider viruses to be the etiologic agents in leukemia but merely a contaminant Recent studies by S O Schwartz *et al* (615b, c) have given impetus to the viral theory of the etiology of leukemia

Furth (206), who did considerable study on animals with leukemia, regarded it to be a neoplastic disease He stated "The essential change in leukemia resides in the leukemic cell and consists of an acquired inability of immature lymphocytes to respond to forces normally regulating their proliferation and maturation This change is essentially that termed neoplastic, and the end result is a new type of cell with a wide range of fixed abnormalities as concerns behavior and appearance" Since leukemic cells resemble carcinoma cells in many ways, there are many investigators who concur with Furth and believe that leukemia is a true carcinoma

Still other investigators believe that either an excess or a deficiency of certain hormones (metabolic disease) is the cause of leukemia It has been shown that cortisone can produce temporary remissions in acute leukemia F Miller *et al* (450b) believed that certain hormones obtained from the urine, serum and feces of patients with leukemia can both stimulate and maturate white blood cells However, these studies have not been confirmed Erf (168b) believed that a deficiency of some intracellular maturating substance is a likely and possible theory for the etiology of leukemia

M Block *et al* (55c) investigated the preleukemic phase of acute leukemia They found that anemia, purpura, and

other blood disorders may precede acute leukemia Allergic manifestations are frequent in "diseases of the blood," a finding confirmed by Block (55c), who noted an increase in drug reactions, asthma and urticaria The summary of their findings was as follows A preleukemic phase, preceding the development of true acute leukemia, described in 10, and possibly 11, cases of acute leukemia and in one case of subacute leukemia Ten of the 12 patients were women, and six had an allergic diathesis Physical examination revealed no abnormalities except for fever, evidence of abnormal bleeding and, occasionally, ulcers of the mucous membranes Palpable enlargement of the hematopoietic organs was usually first encountered after the leukemic phase had begun The preleukemic period, which was much longer than the leukemic period in all but one patient, was marked by deficiency of at least one type of bone marrow function A hemorrhagic tendency, usually accompanied by thrombopenia, was the most frequent early expression of this marrow malfunction Neutropenia occurred comparatively early in the course of the disease and preceded the disappearance of lymphocytes Monocytosis was fairly common, but was difficult to evaluate because of the problem of differentiation from myelocytes Erythroblastosis and reticulocytosis which were sometimes marked, were frequent Immature cells tended to appear in the peripheral blood toward the end of the preleukemic phase, but a peripheral blood picture characteristic of acute leukemia was first noted in the leukemic phase of the disease Biochemical determinations yielded nonspecific results, except for the fairly common finding of hyperbilirubinemia and increased fecal urobilinogen, indicative of hyperhemolysis In the preleukemic phase, the most characteristic early change in the bone marrow was the development of maturation arrest and aplasia of granulocytes, which was accompanied by an erythroblastic tissue which varied from extreme aplasia to extreme hyperplasia There after, progressive hyperplasia and maturation arrest of granulocytic precursors developed, until the marrow was largely replaced by myeloblasts and progranulocytes, which marked

the beginning of the leukemic phase Histologic study of liver and spleen sections, in the preleukemic phase, failed to reveal any marked abnormalities Occasionally, myeloblasts were present in the splenic red pulp immediately prior to the development of the preleukemic stage of the disease The major problem in the differential diagnosis resulted from the resemblance of the preleukemic stage to various other blood dyscrasias particularly toxic neutropenia, aplastic anemia, or hypersplenism This differential problem was not clarified until the leukemic stage developed This stage was almost invariably acute and in some cases, was "explosive" in its course and resistance to the usual palliative therapeutic measures

II

ACUTE LEUKEMIA

ACUTE LEUKEMIA usually appears abruptly in persons who have previously been in good health. The typical course of this disease lasts from one week to three months. The first symptoms are usually weakness, marked pallor, cutaneous or oral hemorrhages, and loss of weight. The patient may com-



Figure 1. Oral hemorrhages in acute granulocytic leukemia.

plain of sore throat, headaches, pains in the bones, and fever. However, marked variations of symptoms may occur in acute

leukemia and for this reason the diagnosis is usually made by a study of the peripheral blood In acute leukemia physical examination usually reveals marked pallor and generalized lymphadenopathy while splenomegaly may or may not be present and the skin may show hemorrhagic manifestations or true leukemic infiltrations Anemia is invariably present in acute leukemia and may be extremely severe Thrombocytopenia is also a characteristic finding the blood platelet count is frequently less than 100 000 per cu mm The most striking changes in the peripheral blood are in the character of the leukocytes and in typical cases there is a predominance of a single type of cell The number of blast cells is frequently so great that the intermediate phases in maturation of these cells are so few that it may be exceedingly difficult to determine whether the blast cells are myeloblasts monoblasts or lymphoblasts When this occurs some investigators have classified this type of leukemia as stem cell" or blast cell" On the other hand Forkner (192a) believed that the three main types of acute leukemia have certain distinctive clinical features He stated that diffuse marked swelling of the mucous membranes particularly of the gingivae usually with ulceration and necrosis is characteristic of acute monocytic leukemia but may be present in acute granulocytic or lymphocytic leu



Figure 2 Swelling of gums associated with acute monocytic leukemia (*A M A Arch Dermat* 73 189 1956)

kemia A diffuse cellulitis with pain, swelling, and inflammation of the deeper tissues of the face, is associated with these lesions In acute granulocytic leukemia the spleen is usually not palpable, in acute lymphocytic leukemia it is enlarged and is palpable three cms or more below the costal margin Generalized lymphadenopathy almost invariably occurs in acute lymphocytic leukemia The lymph nodes, particularly the cervical nodes, may be slightly or moderately enlarged in acute monocytic leukemia, but generalized enlargement, as in acute lymphocytic leukemia, usually does not occur Generalized lymphadenopathy rarely occurs in acute granulocytic leukemia and, when present, is slight

Cutaneous Manifestations

The first report of acute leukemia was by Friedreich (202) in 1857 It was not until 1899, however, that Ebstein (158) published the first account of the outstanding clinical symptoms of the disease, based on a study of 16 cases The onset of the disease in Ebstein's patients was frequently sudden with hemorrhages from the gums and nose and purpuric cutaneous lesions The cutaneous manifestations of acute leukemia may be divided into the nonspecific or toxic lesions and the specific lesions

A. Nonspecific Cutaneous Lesions

1 Pallor Pallor is a marked feature of the acute leukemic state and is probably due to the rapidly developing anemia

2 Hemorrhagic Phenomena Acute leukemia is usually accompanied by spontaneous hemorrhages Tzanck *et al* (691) reported 60 patients with acute leukemia who had abnormal bleeding during the course of the disease with cutaneous and mucosal hemorrhages predominating Petechiae occurred in 57, ecchymoses in 32, and bleeding from the gums and epistaxis in 31 patients In the acute forms this hemorrhagic state is probably dependent to a great extent, upon the paucity of blood platelets The petechial lesions may be generalized or may be limited to one area of the body Frequent

ly they occur in the form of successive crops which appear for no apparent reason The most frequent site of predilection of ecchymoses is in the region of the sacrum In the great majority of cases there is hemorrhage from the gums mani fested by a persistent oozing of blood which according to Ramsay (547) may be a prominent factor in the production of the anemia

The explanation of the tendency to hemorrhages is some what obscure The more severe forms of purpura are generally associated with a marked decrease in the number of blood platelets such as that usually found in lymphocytic leukemia On the other hand there is also a marked hemorrhagic dia thesis in the other forms of leukemia although studies on adults have disclosed that the platelets may be normal or even increased in number

Bleeding of the gingivae appears to be associated with stomatitis as an early manifestation of acute granulocytic leu kemia and consequently occurs more frequently in adults A typical example was described by Nomland (482) This pa tient, a 23 year old woman had complained of fatigue and loss of weight for the past few months During the past two weeks soreness and bleeding of the gums had suddenly de veloped The gums were red spongy superficially ulcerated and bled following the slightest trauma There were scattered cutaneous lesions 1 to 3 mm in diameter which were essen



Figure 3 Hypertrophy of the gingiva (*Eye Ear Nose & Throat Month* 31 309 1952)





Figure 4 Hypertrophy of the gingiva (*Eye Ear Nose & Throat Month* 31 309 1952)

Figure 5 Hypertrophy of the gingiva

tually small hemorrhages The diagnosis was acute granulocytic leukemia

Acute monocytic leukemia occurring in a 47 year old woman was reported by Sydenstricker and Phinizy (669) She had innumerable purplish cutaneous macules from 1 mm to 1 cm in diameter densely scattered over the trunk and thighs and less densely on the legs There were annular, purpuric lesions 2 to 3 cms in diameter involving both arms which were confluent on the extensor surfaces of the forearms Histologic examination of the cutaneous lesions revealed massive infiltration of the corium with large monocytic cells which were most numerous around the sweat and sebaceous glands and in the perivascular connective tissue Generalized purpura associated with acute monocytic leukemia was also described by Weissenbach *et al* (719a)

The cutaneous manifestations of acute eosinophilic leukemia usually consist of hemorrhages such as petechiae of the skin and mucous membranes A 16 year old boy reported by Hay and Evans (266) had subconjunctival hemorrhages as well as purpura on both lower legs Stephens (651) patient presented ecchymotic and petechial cutaneous lesions on the trunk face and extremities and numerous petechiae scattered over the mucous membranes of the mouth and conjunctivae Forkner *et al* (192e) described a 33 year old man in whom generalized cutaneous lesions and hypertrophy of the gingivae with superficial ulceration in some areas developed following extraction of a tooth

3 Oral Lesions The intra oral lesions occurring in acute leukemia are numerous and varied Pathologic processes affecting the mucous membranes are chiefly hemorrhage necrosis and hypertrophy of the gingivae Leukemic manifestations of the mouth are mainly confined to the gingival tissues and mucous membranes according to Moloney (458) The most common lesion is bleeding from the gums which is probably due in part to infiltration of the bone marrow by leukemic cells which crowd out or inhibit megakaryocytes with the resulting blood platelet deficiency In some cases





Figure 4 Hypertrophy of the gingiva (*Eye Ear Nose & Throat Month*, 31 309, 1952)

Figure 5 Hypertrophy of the gingiva

Leukemic lesions of the throat are not as frequent or varied as those which occur in the mouth Waldeyer's tonsillar ring is prone to secondary infection Leukemic tonsillar hypertrophy rarely develops into true gangrene with ulceration according to Philip (520) He stated that in the great majority of instances the gangrene of a leukemic process begins in the gingival mucosa not in the tonsil and may extend from this area into other portions of the mouth or throat Stoker (657) reported a 55 year old man in whom both faucial and lingual tonsils were markedly hypertrophied

4 ERYTHEMA MULTIFORME Acute leukemia frequently begins with the cutaneous lesions of erythema multiforme Hasselmann and Johne (264) reported a 20 year old man who had erythema multiforme as the initial symptom of acute granulocytic leukemia Azerad *et al* (20) described a 58 year old man who had erythema multiforme associated with acute monocytic leukemia Degos *et al* (143b) reported a 44 year old woman who had a history of intensely pruriginous cutaneous lesions These lesions began as extremely pruritic urticarial plaques which were followed in about two days by a generalized bullous eruption Exfoliation of the skin involved the palms and soles Remenovsky (553) described a 51 year old patient who had acute lymphocytic leukemia with a bullous eruption on the wrists and forearms Kanter and Mercer (326) reported a young woman who had acute monocytic leukemia associated with ulcerative vaginitis

5 PRURIGO LIKE PAPULES Papular cutaneous lesions were present in a 16 year old boy described by Stokes and Weidman (658) These pruritic papular lesions which began on the outer surfaces of the legs then became generalized and simulated dermatitis herpetiformis The resemblance of this type of eruption to dermatitis herpetiformis is discussed in more detail under the Nonspecific Cutaneous Lesions of Chronic Lymphocytic Leukemia (Chapter VII)

Della Vida and Connell (146 case 1) reported a 63 year old man who had numerous maculo papular hemorrhagic lesions which had small yellow vesicular centers involving

the bleeding gums are pale and of normal contour In others, the gums are hypertrophic and edematous and resemble the appearance of the gums in scurvy or acute stomatitis, according to Love (397) As the leukemia progresses, the epithelial and submucous layers of the gums undergo exudative and necrotic changes, so that there is sloughing of irregular areas of the lining membrane Such sloughing, according to H W Smith (641), leaves ulcerations that give a foul odor to the breath This foul odor, plus the finding of fusiform bacilli and spirochetes as secondary invaders of the lesion, often leads to a mistaken diagnosis of Vincent's stomatitis

Infiltration of the gums by leukemic cells occurs in acute leukemia and results in swollen gums which are painful and bleed easily on slight trauma At times this swelling is so extreme that the gums cover the teeth Osgood (496a) reviewed the cases of monocytic leukemia and reported that gingival swelling was noted in 80 per cent of 88 cases in which the gums were mentioned Forkner (192a), in a discussion of acute leukemias, stated 'It is my opinion that the clinical picture of diffuse, marked swelling of the mucous membranes, particularly the gingivae, usually with ulceration and necrosis is characteristic of acute monocytic leukemia, and is usually absent in acute leukemia of the granulocytic and lymphocytic type" However, a patient who had acute granulocytic leukemia associated with marked gingival hyperplasia, was reported by Fleury *et al* (189)

The next most frequent oral manifestation consists of areas of necrosis which may appear on the buccal surfaces of the cheeks, on the labial surfaces of the lips, on the gums, on the hard or soft palate, or on two or more of these areas Wiseman *et al* (739b) reported an 11 year old boy who had an extensive sloughing lesion of the left side of the face which caused loss of the entire cheek and the left half of the mandible Pollosson and Lebeuf (534) reported a 56 year old man who had a gangrenous ulceration of the cheek accompanied by a foul odor and high fever Noma occurring in a three year old boy was reported by Hicken and Eldredge (280)

the legs particularly over the tibial areas The arms were covered with red indurated nodules A papulo vesicular eruption confined to the abdomen and back occurred in a 27 year old man with acute monocytic leukemia reported by Lucherini (403) Kohn (348) described a 19 month old girl who had an extensive papulo vesicular eruption involving the groins buttocks and left knee

6 PYODERMA Pyoderma occur frequently in acute leukemias as a result of the reduction in the number of mature granulocytes Schultz (613a) reported a 13 year old boy who presented numerous furuncles on his face and nape of the neck Chickenpox is usually considered to be a relatively mild disease when it occurs in normal children However this disease is very grave when it occurs in a child with leukemia Gerard Marchant (220) believed a possible explanation for this may lie in the fact that in leukemic patients the production of antibodies following an infection or the administration of antigens is extremely defective Another possibility may be the deficiency of gamma globulins in these patients

7 ERYTHEMA A morbilliform cutaneous eruption occurring in a 25 year old man with acute lymphocytic leukemia was reported by Kramer (354) and a scarlatiniform eruption in a 42 year old woman with acute leukemia was described by Lapiere and Compere (370)

8 RARE CUTANEOUS LESIONS Exfoliative dermatitis associated with acute leukemia has been reported by Jaffe (314i) and by Margarot *et al* (428) Herpes simplex is frequently observed as a complication of acute leukemia The toxic process probably acts as the trigger factor in stimulating the virus of herpes simplex

CASE REPORT A 35 year old Negro first had a fever blister on the upper lip six weeks previously followed by a low grade intermittent fever Examination disclosed several small irregular white areas on the retina in the temporal portion of the right fundus and scattered over the superior and temporal portions of the left fundus There were areas of hemorrhage along the

course of the artery in the temporal portion of the fundi, bilaterally The mucous membranes of the throat were pale On examination of the lungs, there was increased dullness over the upper sternal area and extending somewhat to the left at about the level of the second or third rib There were a few scattered respiratory rales The skin in general was smooth, warm and dry There were irregular, flat, somewhat scaly, coalescent lesions on the neck which extended up into the scalp and were lighter in color than the surrounding skin He stated that these lesions had been present for several years At autopsy, five months later, the anatomic and histologic diagnoses were subacute lymphocytic leukemia petechial hemorrhages in the stomach, and multiple bacterial emboli of the spleen kidney, pericardium lymph nodes and adrenal glands

An unusual manifestation of acute granulocytic leukemia was reported by Casilli *et al* (103) in an eight day old infant whose cutaneous lesions simulated those of urticaria pigmentosa

We (561) presented a 69 year old woman who had acute monocytic leukemia and erythema nodosum She first had headache vertigo and nausea following penicillin therapy five years previously and these same symptoms had occurred following the oral ingestion of penicillin three months before admission to the hospital On examination, she had severe respiratory distress considered to be "bronchial asthma," but she responded well to therapy within the first 24 hours She had marked anemia and a sore throat of two weeks' duration One week after admission to the hospital numerous, varied sized painful tender erythematous cutaneous nodules suddenly developed along the medial and dorsal surfaces of both lower extremities Simultaneously, severe pain occurred in the left elbow, both knees ankles and feet These joints were exquisitely tender, erythematous, and slightly edematous Laboratory studies revealed the hemogram to average 48 5 per cent hemoglobin, 2 606 000 red blood cells and 8,390 white

blood cells per cu mm with 33 per cent polymorphonuclears 12 per cent bands 2 per cent eosinophils 5 per cent basophils 37 per cent lymphocytes and 11 per cent monocytes The tuberculin test was negative to a 1/10 000 dilution and positive to a 1/100 dilution The sternal bone marrow findings were compatible with those of acute monocytic leukemia Biochemical studies showed 95 mg/100 cc total cholesterol esters 37 per cent of total cholesterol 8 4 units thymol turbidity and 2 4 gm/100 cc gamma globulin She was treated with 6-mercaptopurine

Blackburn (49) called attention to another clinical sign in acute leukemia He found 73 leukemic patients (51 acute leukemia 22 chronic leukemia) had a peculiar sweet odor to the breath This occurred in 12 of the patients with acute leukemia who did not have obvious clinical involvement of the gums mouth or upper respiratory and alimentary tracts In six of these cases there were signs and symptoms such as splenomegaly to suggest the diagnosis of leukemia but routine clinical examination of the other six patients did not disclose any pertinent findings (other than halitosis) The diagnosis of leukemia was confirmed only after examination of the peripheral blood and sternal bone marrow

B Specific Cutaneous Lesions

Specific infiltrative cutaneous lesions are rare in acute lymphocytic and acute granulocytic leukemia but are characteristic in acute monocytic leukemia When these lesions do occur in acute lymphocytic leukemia they resemble the specific lesions present in chronic lymphocytic leukemia namely nodular or papular small in size and of plum color

P J White and Burns (728) described cutaneous nodules on the abdomen and arm occurring in a three week old infant Dumitresco Mante (156) reported a patient having acute lymphocytic leukemia who had a necrotic cutaneous nodule which had the histologic picture of leukemia Nodular cutaneous eruptions were considered to be the primary manifestations of acute leukemia in a patient described by Payenneville and

Cailhau (511) T Frank (197) reported a 59 year old man with acute lymphocytic leukemia who had brown cutaneous nodules associated with petechiae and purpura Patients having specific cutaneous lesions associated with acute leukemia were described by Wintrobe and Mitchell (733c), Gauld (216), and Schmidt (608) A child who had specific infiltrated cutaneous lesions resembling a fixed drug eruption was reported by Caro (100) and G S Smith's (640a) patient had nodules on the upper eyelids

A patient with acute granulocytic leukemia who had discrete cutaneous nodules on the chest, abdomen and back was described by Warren (708) Jaffe (314g) reported a 74 year old man who had acute granulocytic leukemia with a leukemic cuirasse of the skin in which the "inflections of the skin were quite marked Small, discrete, firm nodules, from one to four mms in diameter, were present on the neck and upper half of the chest A 15 year old girl who had multiple subcutaneous nodules and enlargement of the breasts associated with acute granulocytic leukemia was described by Bonsdorff (65) Joachim and Loewe (318) reported a 38 year old woman who had violaceous nodular swellings over the abdomen, right mastoid region in the axillae, over both thighs, suprascapular region, to the right of the umbilicus, and at the angle of the left mandible

Reimann *et al* (551) reported an infant girl who had congenital granulocytic leukemia with specific cutaneous nodules She appeared to be normally developed and in good health at birth, although there were "knots" in the skin Hemogram revealed 6 900 white blood cells per cu mm Cutaneous nodules continued to develop on the scalp, the trunk and extremities and when she was four weeks of age these lesions were firm discrete and had the consistency of fibromas Histologic study of these lesions suggested "unclassified malig nant tumor," "angioendothelioma with extramedullary hematopoiesis and "fungous infection" The histologic picture showed the lesions to be composed of globoid or polyhedral cells tightly packed in an organoid array This picture did

not resemble leukemic infiltration but there were a few small cells having compact nuclei which were "hesitantly interpreted as hematopoietic" She continued to remain in normal health and the white blood cells numbered 9,000 per cu mm She was 13 weeks old when fever, persistent vomiting, pallor, exophthalmos and lymphadenopathy developed and the cutaneous nodules had increased in size The liver was enlarged and the spleen was palpable Hemogram revealed 3,200,000 red blood cells and 89,000 white blood cells per cu mm, with a preponderance of primitive cells The blood platelets, which previously had numbered 220,000, now decreased to 25,000 per cu mm The bone marrow showed a similar disproportion of granulocytic cells One week later the white blood cells decreased to 40,000 per cu mm and she died This case was one in which cutaneous nodules preceded hepatomegaly, leukocytosis, petechiae, or other clinical signs of leukemia Reimann *et al* believed that cutaneous nodules may be the initial symptom of congenital leukemia and these nodules are histologically characteristic, despite the fact that leukemic infiltration or hematopoiesis is inconspicuous

Congenital leukemia was also reported by Veeneklaas (697) in an infant who had a hepatosplenomegalic syndrome at birth The initial cutaneous lesion was an "angioma like" tumor on the head, but diffuse cutaneous infiltrations subsequently appeared Histologic study of the infiltrated areas and tumors disclosed an infiltration of monocytic cells which contained little protoplasm The hemogram revealed 1,000 000 white blood cells per cu mm, with 98 per cent monoblasts The child died seven weeks later Veeneklaas stated that the more intense blood supply present in neonatal skin may be a possible explanation for the frequency of cutaneous infiltration *which occurs in congenital leukemia, since he found five additional* "proved" cases in the literature

A 37 year old man, presented by Zakon and Sutton (749b), had a generalized, rather severe pruritus which had first developed about three months' previously Two weeks later, a small cutaneous papule appeared on the right side of the jaw

and the following month he had generalized petechiae and small ecchymoses The hemogram revealed 7 1 gm hemo globin 3 720 000 red blood cells and 11 500 white blood cells per cu mm with 73 per cent blast" cells 36 per cent lym phocytes and 1 per cent segmented cells There were 67 000 blood platelets per cu mm The sternal bone marrow studies as well as the hemogram were characteristic of "an acute my

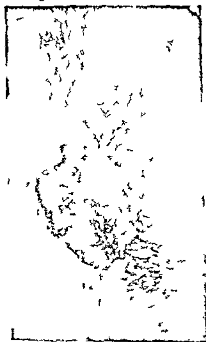


Figure 6 Large ulcerated hemorrhagic lesion on the right mandible

eloblastic process " On examination he had a large ulcerated pruritic cutaneous lesion on the right mandible which had increased rapidly in size since it appeared two months previously There was a smaller but similar lesion in the right submental region He also had bilateral generalized lymphadenopathy

A 20 year old Negro who had multiple cutaneous ulcers, associated with acute granulocytic leukemia, was presented by Webster *et al* (713c). Hoarseness, which had first developed four months' previously, was followed by a sore throat, while chills, fever, and occasional bleeding from the nose appeared later "Lumps" then appeared in the left axillary and inguinal regions, some of which were incised and drained pus Dyspnea occurred, and he had scrotal and perianal ulcerations of three weeks' duration On examination he had multiple cutaneous ulcerations of the scrotum, crural area, and gluteal cleft, which varied in size from a few millimeters to large ulcers which involved both buttocks The borders of the large ulcers were slightly raised and the center was covered by a necrotic eschar He had generalized lymphadenopathy, and the spleen was palpable The hemogram revealed 22 per cent hemoglobin, 1,500,000 red blood cells and 5,450 white blood cells per cu mm, with 58 per cent segmented cells, 22 per cent lymphocytes, 11 per cent myeloblasts, 5 per cent monocytes, 1 per cent band forms, 1 per cent eosinophils, 1 per cent basophils, and 1 per cent myelocytes The sedimentation rate was 7 mm per hour and the hematocrit 12 per cent

Case Report A 26 year old man had been subject to free bleeding following "cuts" and slight bruising of the skin for "many years" He had moderate fatigue and considerable loss of weight for two months and swelling and spontaneous bleeding from the gums for the past five days Following bronchitis, three weeks previously, he had continued to have severe night sweats and a low grade fever in the afternoon On examination, his skin was pale, there was marked gingival bleeding, as well as several bleeding, swollen areas, which were undergoing early necrosis, on the supratonsillar fossa The spleen was palpable one cm, and the liver three cms, below their costal margins There was one enlarged lymph node in the left axilla, one in the right epitrochlear region, and numerous ones in both femoral triangles The hemogram revealed 2,850,000 red blood

cells and 95,000 white blood cells per cu mm, with 10 per cent polymorphonuclears, 10 per cent lymphocytes, 61 per cent myeloblasts, 12 per cent progranulocytes, 4 per cent myelocytes, and 3 per cent metamyelocytes The hematocrit showed 22 per cent red blood cells and 7 per cent white blood cells total 29 per cent The sedimentation rate (uncorrected) was 34 mm per hour. The reticulocyte count was 0 6 per cent Sternal bone marrow studies disclosed a predominance of myeloblasts and an abundance of monoblasts The diagnosis was "acute monocytic leukemia" He continued to have a daily temperature, up to 102 deg F, bleeding from the gums, and crops of petechiae appeared over the lower anterior wall of the chest and shoulder on the right side He died two months later and, at autopsy, the skin was pale The gums were spongy and hypertrophic, with an area of necrosis on the left anterior portion Petechiae and ecchymoses, which were red in color and up to one cm in diameter, were distributed over all cutaneous surfaces The anatomic diagnoses were acute granulocytic leukemia, secondary anemia, and multiple generalized petechial cutaneous hemorrhages

Webster *et al* (713b) presented a 24 year old man who had noted epigastric pain one year previously Roentgenograms revealed an ulcer of the stomach He had lost a considerable amount of weight during the preceding year Following influenza, one month previously, he became very weak, the loss of weight became greater, and left inguinal lymphadenopathy appeared A diagnosis of acute granulocytic leukemia was made and he was given 2 mg of Aminopterin* by mouth The day following this therapy his lower lip became edematous and eight days later, superficial ulcerations developed along the buccal surface of the lower lip and along the gum line On examination, he had small, movable, discrete bilateral cervical lymphadenopathy and axillary, inguinal and epitrochlear lymphadenopathy The liver was pal-

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et al (138 case 1) reported a 45 year old man who had a purplish maculopapular cutaneous eruption involving the face, trunk and extremities Histologic study of a cutaneous papule revealed a leukemic infiltration of monocytic cells Jaffe (314b) reported a 38 year old woman who had specific "punched out" cutaneous ulcers At autopsy the diagnosis was acute monocytic leukemia with leukemic infiltrations in all tissues of the body

C Eosinophilic Leukemia

Eosinophilic leukemia appears to be a rare disease and possibly for this reason is not accepted by all investigators as a distinct clinical entity However there are cases of leukemia which occasionally present a preponderance of the eosinophilic series of granulocytes Whether this type of leukemia is merely a variation of granulocytic leukemia or should be classified as a separate entity is an academic question

The rarity of this condition is apparent in reviews of the subject In 1949 Evans and Nesbit (172b) were able to find only 18 cases of eosinophilic leukemia in the literature and described an additional case In 1953 Rothstein *et al* (584) stated that there were "about" 25 cases in the literature up to that time and they also described one case

The patient reported by Evans and Nesbit (172b) was a 35 year old woman who had pruritic "lumps" on the legs for the previous five years During this time these subcutaneous lesions would disappear for long periods of time and then recur There was wide deep excoriation from scratching which made the lesions difficult to recognize There were firm deep seated masses" in areas not superficially reddened which were not pruritic A diagnosis of dermatitis herpetiformis had previously been made Histologic examination of a cutaneous lesion revealed large numbers of mature eosinophilic granulocytes particularly around the blood vessels Hemogram showed marked leukocytosis with 25 per cent adult eosinophils Examination of the sternal bone marrow revealed the

pable two cms below the costal margin He had moderate hypertrophy of the gums, a "white lesion" on the lateral aspect of the tongue, and a few petechiae on the hard palate There were several superficial erosions along the border of the gums and on the buccal surface of the lower lip A large ecchymotic area, having two crusted, ulcerated lesions, involved the left inguinal region and a large, nonulcerated, ecchymotic lesion was present in the posterior cervical region



Figure 7 Ulcers of the lower lip following Aminopterin® therapy (*Eye Ear Nose & Throat Month*, *31* 309, 1952)

The hemogram revealed 67 per cent hemoglobin, 3,850,000 red blood cells, and 21,000 white blood cells per cu mm, with 49 per cent monocytes, 29 per cent lymphocytes, 13 per cent myeloblasts, 4 per cent band cells, and 3 per cent segmented cells Biochemical examinations disclosed 7 3 mg /100 cc total protein, 6 1 mg /100 cc uric acid, and 34 mg /100 cc non protein nitrogen The sternal bone marrow was hypercellular The number of megakaryocytes was markedly decreased The nucleated red blood cell to white blood cell ratio was 1 6 Erythropoiesis was normoblastic Granulopoiesis was almost completely replaced by myeloblasts The basophils, plasmacytes, and lymphocytes were slightly increased in number The findings were those of acute granulocytic leukemia

Specific papular cutaneous lesions are frequently present in acute monocytic leukemia These specific lesions are discussed more fully under Monocytic Leukemia (Chapter V) Dacie

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total white cells to consist of a very large proportion of eosinophils They concluded that this patient had eosinophilic leukemia and the symptoms became increasingly severe as the eosinophils showed progressive immaturity This 'left shift" eventually became so marked that before death a large proportion of both the peripheral blood and bone marrow cells were myeloblasts At autopsy there was invasion of many of the tissues and organs with mature and immature eosinophilic myelocytes and myeloblasts Rothstein *et al* (584) described a 61 year old woman who presented cutaneous lesions consisting of several ecchymotic areas over the trunk and several petechiae on the legs Following ACTH therapy, there was a marked reduction in the number of eosinophils in the peripheral blood

A 49 year old man who had marked inguinal lymphadenopathy and numerous disseminated cutaneous infiltrations was described by Deme (147) There were 35 000 peripheral white blood cells per cu mm, with 56 per cent eosinophils and the sternal bone marrow showed 62 6 per cent eosinophilic leukocytes, of which 22 per cent were immature forms Histologic examination of the skin disclosed lymphocytic and leukocytic infiltrations with eosinophilic leukocytes and reticulum cells in the cutis and subcutis There was a "leukemic picture' on histologic examination of the lymph nodes Carmel *et al* (98) described a 24 year old man who had received nitrogen mustard and urethane therapy for eosinophilic leukemia On his third admission to the hospital a macular, erythematous cutaneous eruption appeared over the trunk while he was receiving roentgenotherapy This eruption later spread to the extremities and the lesions gradually became raised and infiltrated and eventually some became hemorrhagic Histologic study of the skin was reported to show leukemia cutis Simultaneous to the cutaneous eruption, a septic fever developed and numerous ulcers appeared on the oropharynx, especially over the right lingual tonsil Just before death these ulcerations had spread to involve the entire mouth, causing severe pain and discomfort

W. L. Cook et al (121 case 4) reported a 28 year old man whose initial symptoms were left inguinal lymphadenopathy and fatigue There were 27 000 peripheral white blood cells per cu mm with 47 per cent eosinophils The picture of the sternal bone marrow was consistent with that of eosinophilic leukemia and histologic study of a lymph node showed leukemic infiltration One year later he presented the typical picture of leukemia cutis and a temperature of 103 to 105 deg F following roentgenotherapy

Zubiri and de la Puente (756) reported a 57 year old man who had squamous crustaceous cutaneous lesions following "repeated bites from parasites" These lesions which involved the back chest and arms were accompanied by lichenification and melanoderma of the skin as well as slight fever loss of weight and diarrhea The hemogram disclosed 18 000 white blood cells per cu mm with 61 per cent eosinophils Following removal of the parasites he had a severely pruritic erythroderma with abundant squamous pustules which were distributed in circles There was marked hepatomegaly and the spleen was palpable There was moderate axillary inguinal and cervical lymphadenopathy with periadenitis The sternal bone marrow study revealed eosinophilia There was no improvement following irradiation therapy but nitrogen mustard therapy "cured" the cutaneous lesions and the blood picture was "normalized" However 15 months later he presented papulobullous cutaneous lesions which had an annular distribution and marked peripheral blood eosinophilia occurred Histologic examination revealed eosinophil exocytosis which, in some places gave rise to subcuticular microabscesses and perivascular dermal infiltrates with a great predominance of eosinophils He again recovered following urethane therapy

H L. Hyman and Jarrold (305) described a 34 year old Negro who had marked eosinophilic leukocytosis of from 50 to 66 per cent The clinical studies and the autopsy findings indicated eosinophilic leukemia The predominant cell present in the peripheral blood and bone marrow was an "abnormal" eosinophil In their opinion the presence of this cell in the

peripheral blood and numerous organs suggested that "eosinophilic leukemia is a distinct entity, with clinical and histologic features that set it apart from its very close relative, granulocytic leukemia."

Among 23 cases of eosinophilic leukemia, J. D. Gray and Shaw (240) found the average peripheral white blood cell count to be 76,000 per cu. mm. Among counts ranging from "normal" to more than 200,000 white blood cells per cu. mm. the average number of eosinophils was 63 per cent, with the total counts ranging from 41 to 70 per cent eosinophils. They found that 18 of these 23 patients were men and the age incidence varied from 16 months to 55 years. Among these patients, the duration of the disease was from a "few days" to 14 months in 13 cases, and five patients had lived for more than two years after the onset of the disease.

There have been several reports of acute eosinophilic leukemia. O'Leary (488a) mentioned a patient in whom the disease began as an acute vesicular cutaneous eruption, characterized by periods of severe pruritus which was followed by erythema multiforme-like lesions with "showers of vesicles." The vesicular eruption recurred and sometimes small vesicles, and rarely bullae, covered the greater part of the cutaneous surface, which was markedly pigmented. The hemogram revealed 40,000 white blood cells per cu. mm., with 50 to 55 per cent eosinophils, which persisted for several months. Morphologically, this patient presented a severe dermatitis herpetiformis-like eruption resembling the lesions which occurred in the patient described by Evans and Nesbitt (172b).

The patient reported by Stephens (651) was a 17 year old girl who had small areas of cutaneous "discoloration" for the previous two to three months which were accompanied by gradually increasing pallor and limitation of "exercise tolerance." She had a generalized purpuric eruption which had been present for one week. On examination, she was semicomatose, with marked cyanosis of the face, lips, and nail beds. There was an ecchymotic and petechial eruption involving the face, trunk, and extremities, as well as numerous

petechiae over the mucous membranes of the mouth and conjunctivae

Hay and Evans (266) reported a 41 year old man who presented a "shower" of petechiae on the trunk and legs preceding death The day before he died the hemogram revealed 72 187 white blood cells per cu mm, with 83 7 per cent eosinophils Forkner *et al* (192e) described a 33 year old man who had generalized hemorrhagic cutaneous lesions and slight ulceration over the uvula and pharynx 15 days after extraction of a tooth Five days later the hemogram revealed 158,000 white blood cells per cu mm, with 81 per cent eosinophils

D *Differential Diagnosis of Acute Leukemia*

The following conditions, which have been mistaken for leukemia in children, were listed by Mills (452)

INFECTIONS *(Lymphocytic Response)*
- Pertussis
- Rubella
- Mumps
- Infectious mononucleosis
- Infectious lymphocytosis
- Typhoid fever
- Viral and fungous diseases
- Congenital syphilis
- Tuberculosis
- Brucellosis
- Agranulocytosis
- Collagen diseases (rheumatic fever, dermatomyositis, rheumatoid arthritis, lupus erythematosus)

INFECTIONS *(Myelocytic Response)*
- Bacterial pneumonia
- Meningococcic meningitis
- Osteomyelitis
- Diphtheria
- Sepsis (subacute bacterial endocarditis)

NUTRITIONAL DEFECTS
- Rickets
- Scurvy

Malnutrition

Intoxications

Heavy metal poisoning

Drug poisoning

Severe burns

Exophthalmic goiter

Primary hyperparathyroidism

Malignant Diseases

Neuroblastoma

Hodgkin's lymphoma

Reticuloendotheliosis

Metastatic bone lesions

Severe Bleeding or Hemolysis

Acute and chronic hemorrhage

All hemolytic disorders

Portal hypertension

Conditions mistaken for leukemia occurring in adults would include

Lymph Nodes

Tuberculosis

Hodgkin's disease

Lymphosarcoma

Sarcoidosis

Malaria

Splenomegaly

Hodgkin's disease

Banti's disease

Hemolytic anemia

Sarcoidosis

Malaria

Hemorrhagic Manifestations

Purpura hemorrhagica

Aplastic anemia

Scurvy

Cutaneous Nodules

Hodgkin's disease

Sarcoidosis

Lymphosarcoma

Mycosis fungoides

Kaposi's sarcoma

Neurodermatitis of the scalp (Zakon and Eirinberg 749a, Ayres, Jr and Ayres, III 19)

ULCERS OF THE PENIS (Bluefarb and Webster 56m)

Syphilis
Lymphogranuloma venereum
Granuloma inguinale
Tuberculosis
Carcinoma
Erosive balanitis

Seven patients having neurodermatitis of the scalp were reported by Ayres, Jr and Ayres, III (19) All of these patients had one or more persistent, pruritic nodules of the scalp which were somewhat refractory to local therapy The clinical course, appearance of the lesions, and histologic findings, suggested the probability that this entity, which apparently is not commonly recognized, is a variant of localized neurodermatitis Zakon and Eirinberg (749a) presented a patient who had "turban like" tumors of the scalp which had a histologic picture resembling that of "lymphoblastoma" It was at first believed that the early "turban" tumors were secondary metastases of some visceral carcinoma However, subsequent histologic examination revealed a lymphocytic infiltrate The peripheral white blood cells numbered 8,000 per cu mm, with 11 per cent eosinophils, and the sternal bone marrow revealed 16 per cent eosinophils

E *Treatment of Acute Leukemia in Children*

1 GENERAL MEASURES S Farber (178a) employed the concept of "total care" for the patient with leukemia This term is used to describe the best medical and surgical treatment available at the present time for the comfort, well-being, and increased survival of a patient having an "incurable" disease This "care" includes the use of blood transfusions, fluids designated to restore the acid base equilibrium and the proper hydration of the tissues, antimicrobial agents for the prevention and treatment of complicating infectious disease, local or generalized irradiation, and surgical measures, even for the temporary relief of symptoms resulting from obstruction

or pressure Measures to bolster the mental state of the patient and his family and friends should also be given consideration This "total care" will not tend to alter the prognosis, however

Farber (178a) stated that the three problems presented by a child having leukemia are hemorrhage, complicating secondary infections, and the leukemic tumor, with infiltration of most of the organs or tissues of the body The most effective treatment for hemorrhage is the restoration of the bone marrow to an approximately normal state He believed that infection should be prevented or treated vigorously with antimicrobial agents if these children are to survive long enough for anti leukemic chemical or hormonal therapy He suggested therapy to destroy the leukemic cells in the bone marrow and cause rapid disappearance of the infiltrates from the viscera in order to prevent permanent damage to important viscera and possible destruction of the bone marrow

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further treatment The toxic reactions to these drugs may be severe They may consist of severe bone marrow depression with thrombocytopenia and leukopenia, alopecia stomatitis with buccal ulcerations, and extensive gastrointestinal ulceration with bleeding Hyperpigmentation developed in seven out of 10 children having acute leukemia who were treated with Aminopterin and reported by Waisman *et al* (702) Although these reactions are difficult to counteract, citrovorum factor (folinic acid) in daily doses of 5 to 10 mg offers a specific antagonist to these drugs A complete discussion of the folic acid antagonists was presented by Petering (518) Burchenal and Krakoff (84b) preferred to use Amethopterin rather than Aminopterin for the treatment of acute leukemia They noted less toxicity and better therapeutic results from the use of the former drug

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Stickney and Mills (654) stated that corticotropin and cortisone exert no significant effect on normal human bone marrow These hormones, with the folic acid antagonists, constitute an addition to the therapeutic agents available for the treatment of acute leukemia Remissions were produced in 25 per cent of children having acute lymphocytic leukemia when these hormones were used The results were described as "spectacular" but the remissions were not of long duration

IV COMBINED THERAPY Dameshek (139d) noted remissions in 25 of 28 children treated with aminopterin combined with large doses of corticotropin He believed that combined therapy offered the following advantages (1) Corticotropin appears to enhance the effects of aminopterin, (2) the chance of remission is greater than with either agent used alone, (3) the buccal and gastrointestinal ulcerations are diminished in frequency, (4) the bleeding tendency of acute leukemia is diminished by the corticotropin and, (5) the chance for bone marrow aplasia appears less than with aminopterin alone

Kass (330) reported 19 children who were treated for acute leukemia during a two and one half year period There were 13 boys and 6 girls, from three months to 13 years of age, who were treated with antibiotics and all except one were given repeated transfusions of whole blood The duration of survival after establishment of the first symptoms was about three and one-half months for the eight patients who were not given aminopterin and six and one half months for the 11 who received aminopterin, nine of whom also received corticotropin and some also cortisone Two patients had complete remissions of two and one half and three months, respectively, after 19 courses of treatment with aminopterin Of two patients treated with combined aminopterin corticotropin, one had a partial remission for three weeks following therapy Among eight patients treated with 13 courses of corticotropin and two of cortisone, three had complete remissions for from three to six weeks and seven had partial remissions for up to two months

single dose by mouth With higher dosage, formed elements of the bone marrow may be severely depressed, although some patients tolerate 5 to 7 mg per kilogram each day with no toxic effects or only slight gastrointestinal disturbances They reported that 29 per cent of 154 children treated with cortisone and Amethopterin lived at least a year, while 52 per cent of 52 children survived one year or longer when 6 mercaptopurine was added to this regimen The drugs were used in sequence They concluded that when a patient is in the terminal acute stage of chronic granulocytic leukemia, 6 mercaptopurine occasionally produces short remissions The drug is not useful in such conditions as chronic lymphocytic leukemia, lymphosarcoma, Hodgkin's disease, or metastatic carcinoma

III STEROIDS The adrenal hormones (cortisone, hydro cortisone, prednisone) and corticotropin (ACTH) are some times effective in the control of acute leukemia, according to Pearson *et al* (513) Fessas *et al* (184) studied the effectiveness of hormone therapy in 47 cases of acute leukemia They observed excellent results in the lymphoblastic type, complete remissions occurring in 18 out of 22 children (82 per cent) who were 10 years of age or less and in three out of nine older patients There were partial remissions in another seven patients and only three failed to respond to therapy In contrast, there were no complete remissions among 15 cases of acute granulocytic leukemia, *and only two partial remissions* The treatment did not benefit one case of acute monocytic leukemia In some cases it appeared that the leukemic process was accelerated by this therapy These observations would suggest that hormone therapy should be reserved for the lymphoblastic variety of acute leukemia and that such therapy may be contraindicated in the other forms of acute leukemia

The initial doses are fairly large 300 to 400 mg of cortisone, 60 to 80 mg of prednisone, or 200 mg of corticotropin may be administered daily

III

LYMPHOCYTIC LEUKEMIA

A. History

In 1876 Biesiadecki (46) was the first to describe a patient with leukemia cutis In 1880, Philippart (521) reported a 40 year old woman who first presented a cutaneous nodule on the right temple, followed by "pea to egg" sized cutaneous and subcutaneous nodules on the head and face, which resulted in a leonine facies She also had nodules in the breasts She died four years after the initial cutaneous nodule appeared Two years later, Galliard (209) described a 37 year old man whose initial cutaneous lesion was on the chest Three weeks later, numerous, thickened, hard, pale copper-red lesions appeared on the face The forehead was deeply furrowed the eyelids greatly thickened hard, immovable, and covered nearly the entire eyeball, causing a leonine facies The hemogram revealed an "aleukemic phase" with 1,200 white blood cells per cu mm A similar case was described by Kaposi (328a) in 1885 which he designated "lymphodermia perniciosa" Another report prior to 1890 was that of Hochsinger and Schiff (289)

The symptoms of chronic leukemia are generally referable to (1) a local accumulation of cells which cause symptoms by mechanical means, such as marked splenomegaly, cervical and axillary lymphadenopathy, cutaneous tumors, and (2) symptoms referable to a diminution of formed elements of the blood caused by the myelophthisic replacement of the normal cell elements with the leukemic cell The various

F. Treatment of Acute and Subacute Leukemia in Adults

1 Supportive Therapy This therapy includes (1) antibiotics for cutaneous infections, kidney infections, or ulcerations of the mouth and throat, (2) blood transfusions for anemia, and (3) attention to fluid and electrolyte status

2 *Specific Therapy* a Antimetabolites *6-Mercaptopurine* (*Purinethol*®) 6 mercaptopurine was used by Burchenal *et al* (84c) for the treatment of 18 adults having acute leukemia Four of 12 patients who had adequate therapy showed clinical and hematologic improvement 6 mercaptopurine is available in 50 mgm scored tablets The drug may be administered at any time of the day and the entire daily dosage is usually given at one time The dosage for adults is 100 to 200 mg a day Remissions have occurred from three to four weeks after the beginning of treatment It is important to continue maintenance therapy during periods of remission to prevent relapse

Folic Acid Antagonists There are reports of remissions following the administration of Amethopterin (Hays *et al* 268 and Ellison 164) Amethopterin is given by mouth and the usual initial dose for adults is 5 to 10 mg daily The toxic manifestations may be lesions of the mouth (ulcerations), diarrhea, or bone marrow depression

b Steroids Corticotropin and cortisone have been reported to have induced short remissions in about one third of the cases treated The preparations of the adrenal steroids usually employed are ACTH given intravenously (25 to 40 mg over an eight to 12 hour period), ACTH or gel, or zinc ACTH, given intramuscularly (100 to 200 mg a day), and cortisone (200 to 400 mg a day), or hydrocortisone (160 to 320 mg daily) administered orally The salt intake of the patient should be limited and potassium chloride is given routinely

syndromes associated with anemia, such as granulocytopenia, manifested by lessened resistance to infection, and thrombocytopenia, manifested by a hemorrhagic tendency, are all characteristic of the second group General symptoms may include tachycardia, increased sweating, loss of weight, "nervousness," and easy fatiguability

B Pathogenesis

1 *Incidence of Cutaneous Lesions.* The majority of investigators agree that specific cutaneous manifestations occur more frequently in chronic lymphocytic leukemia than in other types of leukemia This belief may be due perhaps to the greater frequency of lymphocytic leukemia At the Cook County Hospital (Chicago), the incidence of chronic lymphocytic leukemia is greater than all other types of chronic leukemia and cutaneous manifestations are frequent in this form However, there is a much higher incidence of cutaneous involvement in monocytic leukemia, although the total number of cases is much lower

In a review of the cutaneous manifestations associated with lymphocytic leukemia Beek (39a) stated that it is not yet known why some patients with leukemia have changes only in the peripheral blood, bone marrow, or other internal organs without cutaneous manifestations, while others have numerous cutaneous manifestations which are sometimes the only clinical symptom of the disease He believed that although leukemic cutaneous changes are rare, all cases having these manifestations should be reported since this problem cannot be adequately studied from occasional case reports

The various cutaneous manifestations occurring with the different forms of lymphocytic leukemia were compiled by Beek (39a) with reference to a connection between these lesions and the type of leukemia The first group comprised patients having normal peripheral blood counts, the second, those with "aleukemic" white blood cell counts up to 10,000 per cu mm, the third, those having "subleukemic" blood counts with 10,000 to 30,000 cells per cu mm, and the fourth,



Figures 8, 9 and 10 Marked lymphadenopathy in lymphocytic leukemia

In Beck's series of patients having cutaneous manifestations associated with lymphocytic leukemia, the age was 55 to 64 years which is 10 years more than the age of selection for all other cases of lymphocytic leukemia He also found that 69 per cent of these patients were men, 67 per cent of whom had cutaneous tumors, 64 per cent prurigo like papular lesions, 87 per cent herpes zoster, 75 per cent bullous lesions, 73 per cent purpura, and 71 per cent erythroderma Among the combined cutaneous manifestations, Beck found the following incidence

COMBINED MANIFESTATIONS PER CENT

Cutaneous Lesion	*Tumor*	*Papule*	*Zoster*	*Bullae*	*Purpura*	*Urticaria*	*Erythroderma*	*Varicelliform*
Tumor	xx	15	48	17	17	50	12	11
Papule	6	xx	4	62	17	12	0	0
Zoster	8	2	xx	0	8	0	0	89
Bullae	5	26	0	xx	17	0	0	0
Purpura	2	3	4	7	xx	0	0	0
Urticaria	3	2	0	0	0	xx	0	0
Erythroderma	6	0	0	0	0	0	xx	0
Varicelliform	1	0	32	0	0	0	0	xx

From these statistics, it appears that lymphocytic leukemic tumors occur with all other cutaneous lesions but most frequently with herpes zoster, when they are usually localized in the healed gangrenous zoster scars Similar localization of these tumors in areas of preceding infection following a local irritating agent have been described by Szentkiralyi (670) and Fuhs (205), or ulcus molle, reported by Szodoray and Borza (672)

This Kobner like phenomenon was found to occur in 8 per cent of the cases having cutaneous tumors associated with lymphocytic leukemia and in 8 per cent of the cases the tumors were ulcerated The tumors were localized on the head in 64 per cent of the cases, on the extremities in 53 per cent, on the trunk in 40 per cent, on the mucous membranes in 14 per cent, and on the tonsils in 15 per cent Leonine facies were found in 5 per cent of the cases There appeared

patients having typical leukemic white blood cell counts Beck's findings are listed as

Cutaneous Lesion	*Normal*	*kemic*	*leukemic*	*Leukemia*	*pleno megaly*	*Hepato-megaly*
Tumor	11	11	22	56	27	15
Papule	2	11	34	53	20	12
Zoster	0	0	8	92	28	15
Purpura	8	18	25	67	40	10
Erythroderma	0	14	39	47	20	12
Bullae	0	10	17	74	23	10

Among the patients having normal peripheral blood findings in Beck's series, leukemic cutaneous changes occurred only in those having lymphocytic leukemic tumors However, these were all instances of true primary cutaneous lymphocytic leukemia

A diagnosis of primary leukemia cutis is made only when there are no changes in the peripheral blood, lymph nodes, or internal organs, and the only symptoms are in the skin A diagnosis is possible only by histologic examination of the cutaneous lesions and thus diagnosis is later verified by the clinical course of the disease Beck found these characteristics to be present in the cases described by Pollosson and Lebeuf (534) and C J White (726) In the cases reported by Abramowitz (1a, b), Grosglik (245a), Halter (257), Kren (356) and Zeisler (750b), there was cutaneous lymphocytic leukemic infiltration, usually localized on the head However, further course of the disease did not show lymphocytic leukemic involvement of the peripheral blood, lymph nodes, or internal organs

Beck (39a) found that cutaneous manifestations were more frequent in lymphocytic leukemia than in other types of leukemia He noted only 72 cases of granulocytic leukemia with cutaneous manifestations reported up to 1948, while there were 289 cases of lymphocytic leukemia with cutaneous lesions He reported that leukemia may occur at any age and in either sex However, Ward (707) and Minot *et al* (454a) noted the definite age of selection was 45 to 54 years

passive infiltration from the blood stream (1) All the morphologic constituents of the blood can be demonstrated in the tumor substance, (2) the channels of transmigration can be ascertained in section (3) the infiltrating cells take up a position in conformity with the planes of least resistance, (4) no cells of reactive type, such as plasmacytes or giant cells, can be demonstrated in the nonulcerated lesions (5) no degenerative changes are demonstrable However, Jaffe (314c) was of the opinion that it is difficult to settle this question, since lymphoid tissue is present in practically all parts of the body Butler (89) described numerous mitoses present in the lymphocytic nests which would indicate local proliferation of the nodules He believed that, even though the primary changes might occur elsewhere, the fact would remain that an independent lymphatic hyperplasia exists in the skin Accordingly, the skin may independently undergo lymphoid transformation which would be contributory to the development of lymphocytic leukemia Mitosis in the cutaneous lesions of chronic lymphocytic leukemia were described by Arndt (14b) Butler (89) stated that numerous mitoses may be present in the diffuse type but are rarely present in the circumscribed type of lymphocytic leukemia cutis However, Ketron and Gay (338a) were unable to demonstrate mitoses in the circumscribed type

Gates (214) believed that the cutaneous tumors occurring in leukemia are of metastatic *origin in the majority of cases* These tumors arise as the result of chance location of diffusely disseminating tumor cells which, when involving the skin act as an independent entity and therefore, there *is no consistent* relationship between the growth of the cutaneous tumors and those in other parts of the body Gates stated that lymphoma and leukemia differ from other forms of malignant growth primarily because the involved cell is mobile rather than stationary thus greatly facilitating the dispersal of tumor cells which may result in widespread distribution through the lymphatic system and blood vessels Temporary thrombosis by tumor cells with gradual extension into adjacent tissue would explain many phenomena, although there *is rarely histologic*

to be no particular localization of the lesions in the older age groups

Rendu (554) observed 100 cases of lymphocytic leukemia and found that 20 per cent had cutaneous manifestations

According to Piney (524a) all instances of specific leukemia cutis occur in the aleukemic form of the disease although a leukemic blood picture may supervene He believed that the specific cutaneous infiltrates which occur in chronic lymphocytic leukemia vary markedly in frequency Granulocytic leukemia cutis probably never occurs without peripheral blood changes whereas specific cutaneous lesions nearly always develop with "aleukemic lymphocytic leukemia Beek (39a) found that 56 per cent of the patients having cutaneous tumors of lymphocytic leukemia had leukemic hematologic findings and 44 per cent had an "aleukemic" blood picture H E Freeman and Koletsky (199) reported that specific cutaneous lesions occurred in 10 per cent of monocytic 8 per cent of lymphocytic and 1 per cent of the granulocytic leukemia cases Among 123 cases of leukemia which were followed to termination J D Kirschbaum and Preuss (343) found five (4 per cent) had cutaneous infiltrations and five (4 per cent) had involvement of the oral cavity Specific cutaneous lesions were present in 8 3 per cent of E Epstein and MacEachern s (166) series of patients who had leukemia

Two important physiological properties which influence the conception of tumors of lymphoid tissue were given by Ewing (174) (1) Lymphoid tissues are relatively mobile rather than fixed and lymphocytes are not only ameboid but are structurally placed in easy access to lymph and blood paths Therefore *tumors and tumor like processes are frequent in lymphoid* tissues and usually tend to become widely diffused (2) Lymphoid tissue responds to irritation with inflammatory hyperplasia far more actively than any other tissue

The question of whether lymphocytic leukemia may originate in the skin as a primary disease or whether the cutaneous lesions are metastatic in origin has been considered Nekam (471) believed that true leukemic tumors were the result of

merous peripheral white blood cells It is generally agreed that several determining factors are apparently involved

According to Piney (524a) lymphocytes are usually found in the great majority of persons in small aggregations in the subcutaneous tissue but these minute masses are very few in number Less frequently a few lymphocytes having no focal arrangement may be scattered in the tissues of normal skin He believed these two modes of distribution would explain the occurrence of the two types of leukemia cutis as well as the rarity of the diffuse type Although the amount of fibrous tissue is always increased in these conditions it is widely distributed in the diffuse type resulting in universal thickening and inelasticity of the skin Thus cutaneous thickening is also increased by obstruction of the lymphatic channels which he believed may also be the possible cause of the intense erythroderma Pinkus (525) was of the opinion that the cutaneous nodules are derived from the normal lymphatic tissues of the skin and are not the result of diapedesis from the peripheral blood Rossle (580) reported a patient with chronic lymphocytic leukemia who had no involvement of the lymph nodes although there was a generalized leukemic cutaneous infiltration It was believed that hyperplastic *reticulum* gave rise to the lymphocytic cells

The presence of reticuloendothelial cellular elements in practically every part of the body permits the development of specific lesions within any structure according to Friedman and Meyer (201) They pointed out that the dosage of radiation therapy should be kept to the *minimum necessary* for relief of symptoms because of the widespread distribution of the disease

The widespread occurrence of minute masses of lymphatic tissue present in the body was emphasized by Ribbert (558) The proliferation which is characteristic of the "hemoblastoses" does not affect all tissues simultaneously and cutaneous involvement at least in the "lymphadenosis" occurs only in the chronic form he stated The two *most* frequent types of specific cutaneous lesions which occur in lymphocytic leukemia

evidence of thrombosis The tumor cells are confined to the perivascular regions in the lower vascular portions of the cutis in the earliest lesions In leukemia, the cutaneous vessels may be filled with cells, while intravascular tumor cells are not usually present in lymphomas Gates assumed that the same factors present in metastatic carcinoma *may occur in* metastatic leukemia and lymphoma The potentialities for growth of metastatic tumor cells are variable and unpredictable Many translocated cells, perhaps the majority, disintegrate and die while the surviving ones may either produce secondary tumors or remain latent for a long period before proliferating The dispersal through the lymphatic and vascular system of the cutis of tumor cells having varying potentialities for growth (together with edema and inflammatory reaction from cellular disintegration) seems, in Gates' opinion, to be adequate explanation for the prodromal cutaneous manifestations, as well as for the tumors of leukemia and lymphoma

There does not appear to be any clear understanding about the relationship between the cutaneous tumors and leukemia and the underlying leukemic process Neither has the relationship between the number of peripheral white blood cells and the appearance and growth of the tumors been consistent In the patient reported by Goldsmith (233a), cutaneous tumors continued to develop and a large ulcerated tumor increased rapidly in size despite the fact that the peripheral white blood cells decreased from 290 000 to 19 000 per cu mm Walther and Strocka (706) mentioned a case in which the cutaneous tumors disappeared during periods of leukopenia but recurred when the peripheral white *blood cells* increased in number The patient described by Westphall (723) had intermittent fever When the temperature was elevated, the lymph nodes became enlarged and the cutaneous tumors decreased in size, while a decrease in temperature resulted in diminution *in size of the lymph nodes* and the cutaneous tumors increased in size and number Cutaneous tumors do not appear to result from simple diapedesis or from infiltration of the tissues coincident with the presence of nu-

literature, to consider leukemia in the group of malignant tumors. However, he did not believe this assumption to be warranted because of the fundamental differences between leukemia and malignant tumors. Malignant tumors metastasize from the primary tumors, while leukemic infiltrations develop locally from the undifferentiated mesenchyme which is distributed widely throughout the body, particularly around the smaller blood vessels. This undifferentiated mesenchyme can normally develop to free histiocytes, and probably to lymphocytes and plasmacytes, when irritated. However, in leukemia a fundamental change occurs in the reactivity of the mesenchyme in that a slight, physiologic stimulation will induce an abundant proliferation of perivascular cells, which may differentiate into lymphocytic and granulocytic tissue. Therefore, the leukemic tissue develops locally and not by metastasis from a primary focus. Leukemic cell proliferation usually involves the bone marrow, spleen, lymph nodes, liver, lymphatic tissue of the gastrointestinal tract, and the kidneys, although there may be more generalized proliferation in some cases with involvement of the heart, adrenal glands, lungs, skin or other structures. Jaffe believed the mesenchyme of the nervous system involved by leukemia did not differ from the mesenchyme of uninvolved areas of the body. Because of the toxic" changes in the brain in acute leukemia a close relationship exists between infection and leukemia according to Jaffe. He believed there may be an "inherited or acquired irritability of the mesenchyma" which causes the "leukemic tendency" to become manifest under the influence of a variety of toxic or infectious agents.

Nekam Jr (472b) favored the theory of "postembryonic capacity on the part of the perivascular lymphoid cells of adventitial origin which was originally advanced by Arndt (14a). Nekam therefore, attributed the development of cutaneous lymphocytic leukemia to an autochthonous origin.

Leukemia cutis as the first manifestation of the disease was reported by Beek (39a) to occur in nearly 50 per cent of the cases of leukemia. In these cases the peripheral blood pic-

are nodular and diffuse and have similar histologic changes However, in the nodular form the masses of lymphocytes have a focal arrangement, whereas they are diffusely distributed in the tissue in the diffuse type According to Piney (524a), this difference in the arrangement of the infiltration is dependent upon the variations in the distribution of lymphatic tissue in the normal subcutaneous tissue

The theory that the nodular cutaneous lesions may originate from hemorrhages from the smaller blood vessels was disputed by Ward (707) because (1) the nodular lesions do not resemble obvious hemorrhage in similar tissues, they do not contain blood pigment, (2) the cells present in the nodules are not distributed in the "promiscuous fashion" which would occur with hemorrhage, and (3) cutaneous hemorrhage is not followed by nodular lesions

Gans (210i) stated that the conception of infiltrating cutaneous tumors resulting from lymphocytic and granulocytic migrations is no longer considered to be correct, whereas the theory of autochthonous development has been accepted and is supported by Ribbert's theory on the ubiquitous presence of lymphatic tissue The foci of lymphocytic cells usually occur in minute numbers and begin to proliferate as the result of leukemic toxins, just as they do in similar tissue in other organs Nekam (471) and Arndt (14a) demonstrated numerous lymphocytes and lymphoblasts in the process of nuclear division, thus proving that migration of the cellular elements from the vascular system and their proliferation in tissue are possible The cutaneous changes in lymphocytic leukemia may be explained by the presence of lymphocytic cells in the skin, while the granulocytic cells in the immature state in which they occur in the peripheral blood, are not found in granulocytic cutaneous lesions according to Gans (210a) Therefore, he presumed that autochthonous development of the extramedullary granulocytic tissue occurs, although there is no certainty as to whether this arises from the endothelium of the blood capillaries or from the cells of the adventitia

Jaffe (314e) found that there is a tendency, in contemporary

taneous leukemic tumors

Semon (623) stated that cutaneous involvement may occur in some cases and involvement of the internal organs or lymphatic tissue may occur in others because these organs are manifestly selected by the infiltrating cells possibly because of an irritating factor He described a patient who had cutaneous involvement limited to the face ears and dorsum of the hands for 7 years He believed this localization would suggest irritation by actinic rays such as occurs in erythema multiforme and lupus erythematosus Rolleston (572a) observed a patient who had widespread papular cutaneous lesions which were preceded by "rigors" on two separate occasions following roentgenotherapy

2 *"Aleukemic" Leukemia* The most comprehensive description of this so called "aleukemic" phase of leukemia is that of Wiseman (739a) He stated that with rare exceptions the histologic picture of the lymphatic tissues is identical with that of lymphocytic leukemia with lymphemia but the peripheral blood shows either no distortions or only minor ones in the total white blood cells and/or the differential count On close inspection however qualitative changes in the lymphocytes of the peripheral blood may usually be noted these changes being identical with those present in lymphocytic leukemia with lymphemia The importance of recognizing this type of leukemia aside from the theoretical implications, lies in the fact that the clinical course and the prognosis may be predicted with reasonable certainty and also more exact and adequate therapy may be given In this type of leukemia it is especially important to understand that therapy should be directed toward the fundamental disease and not according to the changes in the peripheral blood

With regard to the absence of superficial lymphadenopathy as an indication that there is no leukemic infiltration in the deeper lymph nodes several illustrative cases have been described In one of Fraser's (198b) patients the initial lesion apparently developed in the skin and at autopsy was found to have the primary involvement in a group of retroperitoneal

ture was not yet characteristic and was described as the "aleukemic" phase of chronic lymphocytic leukemia However, the cutaneous lesions are not necessarily the first symptom of the disease in patients having a normal peripheral blood picture It has been stated that leukemia cutis is always secondary to other leukemic involvement which, on careful examination, will be evident in either the spleen, liver, bone marrow, or lymph nodes This assumption does not appear to be correct, in that numerous cases of leukemia cutis have been described in which there was no postmortem evidence of leukemic involvement of these particular organs

Wile (731a) believed that exfoliative dermatitis may act as an irritant to the skin and give rise to lymphocytic leukemia He described a patient who had exfoliative dermatitis for six years prior to the development of lymphadenopathy and the peripheral blood picture of lymphocytic leukemia He (731c) later stated "I believe the skin pathology rather than reflecting systemic changes, may be a continuous insult as a causative factor in the production of lymphadenotic changes" Leukemic infiltrations occasionally develop in the cutaneous scars following herpes zoster (Chapter VII) The occurrence of zoster following an insect bite was reported by Drake (153), following burns, as in Halle's (255) patient, and I have observed it following a tuberculin test A patient who developed cutaneous leukemic infiltrations at the site of injections and surgical incisions was reported by Cleland (115) He concluded that local cutaneous infiltrations are of metastatic origin E Epstein and MacEachern (166) reported a woman with leukemia who had a contact dermatitis from tincture of iodine Numerous specific cutaneous nodules soon appeared in the area of dermatitis which evolved into a plaque found to be infiltrated with leukemic cells, on histologic examination The lesions have been reported to follow an infection, as described by Szentkiralyi (670) and Fuhs (205), and following a soft chancre, as noted by Szodoray and Borza (672) According to Beek (39a), this Kobner-like phenomenon is present in 89 per cent of the cases having cu-

ture of lymphocytic leukemia then developed in the sternal bone marrow, followed by similar changes in the peripheral blood

C. Specific Cutaneous Lesions

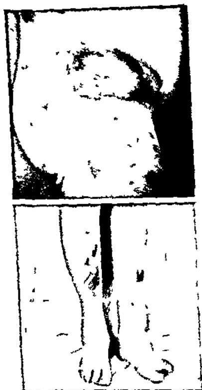
The various specific cutaneous lesions which may be associated with chronic lymphocytic leukemia are (1) nodules, (2) infiltrations or plaques (3) ulcerative lesions, or (4) exfoliative erythroderma The characteristic papules or nodules are blue or red in color The infiltrations may result in thickening or wrinkling of the skin and when the face, especially the cheeks and forehead, are involved, the large folds and grooves produce an appearance described as "resembling the convolutions of the brain" Not infrequently, deep cutaneous ulcerations resembling a gumma occur When generalized erythroderma is present, the skin is dry, scaling, reddened, thickened and pruritic These same specific cutaneous lesions may also occur in other lymphomatous diseases, such as Hodgkin's disease or lymphosarcoma

1 *Nodules* As a rule, the cutaneous nodules are well defined slightly elevated, smooth, and semi globular, and vary markedly in size They may be one mm. in size or as large as 10 cms and the larger tumors frequently become lobulated from coalescence of the smaller nodules Ringed, festooned lesions, resulting from central involution spreading of a single patch, or juxtaposition of individual smaller patches, is an unusual occurrence in lymphocytic leukemia although it frequently occurs in mycosis fungoides The cutaneous tumors are usually persistent but occasionally they disappear spontaneously, or sometimes following roentgenotherapy. According to Gates (214), this is due partly to "local conditions, since growth and regression may occur simultaneously in adjacent tumors or even in the same tumor" The skin which has been involved by a tumor is slightly pigmented or atrophic following complete regression of the tumor A single tumor may show great variability in reaction, at times it "may be sensi-

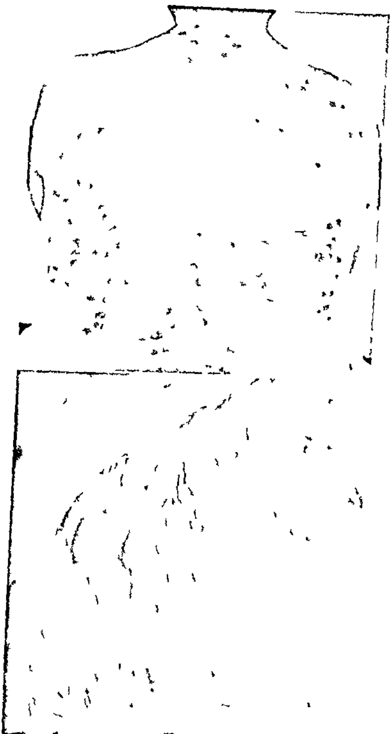
lymph nodes Fraser (198a) believed the fact that fundamental changes of leukemia occur in the tissues and not in the blood is overlooked by many clinicians Among 76 cases in Videbaek's (698b) series, cutaneous infiltrates were the initial symptom in 10 cases Rossle (580) reported a patient who appeared to have primary cutaneous involvement of lymphocytic leukemia in that there was no apparent involvement of the lymph nodes Traub's (688b) patient also presented the first manifestation of chronic lymphocytic leukemia in the skin Scott (617) described a 64 year old woman whose primary lesions were 1 to 10 cm subcutaneous nodules The peripheral blood count was normal and there was no lymphadenopathy or splenomegaly The initial nodule, which appeared on the right frontal area of the scalp, was found, on histologic study, to be a "reticulosis with dense lymphoreticular infiltrate of the stem cells, lymphoblasts and lymphocytes" The typical pic-



Figure 11 Cutaneous nodules of lymphocytic leukemia



Figures 14 & 15 Cutaneous nodules of lymphocytic leukemia



Figures 12 and 13 Cutaneous nodules of lymphocytic leukemia



Figure 16 Leukemic nodule of eyelid

tive and at other times resistant," as in the cases described by Ketron and Gay (338a) and by S W Becker (38) If a concurrent hemorrhagic diathesis occurs, the nodules may be hemorrhagic and simulate a melanoma When the nodules are localized only in the deep portion of the cutis or in the subcutaneous tissue the surface of the lesions may appear normal or have only a slight bluish tinge The typical nodules are yellowish brown or yellowish red to bluish red or purple in color and often appear translucent on pressure These nodules usually develop slowly and rarely become ulcerated In cases having ulceration this was found to be due to trauma and/or sepsis The nodules are usually soft or firm elastic, and edematous while they invariably remain localized to the skin or subcutaneous tissues and the deeper structures are not involved The cutaneous nodules may grow rapidly in size for a time and then remain stationary for years, or they may regress following therapy, without scar formation These nodules usually do not ulcerate and rarely become necrotic The surrounding skin is usually atrophic glossy, and traversed by telangiectases Cutaneous atrophy also occurs in areas not involved by tumors thereby simulating acrodermatitis chronica atrophicans, while in other instances it may resemble scleroderma or dermatomyositis The subjective symptoms usually consist of a "burning" sensation and slight pain or discomfort on pressure Pruritus is not a prominent feature

Although the cutaneous lesions may occur at any time in

rarity, as well as their similarity to other processes However, clinical differentiation is not difficult, as a general rule, because of the certain well known characteristics of the lesions A number of diseases must be considered in the differential diagnosis of cutaneous nodules The patient reported by Barnes and Moffatt (27) had lesions which appeared translucent on pressure, simulating lupus vulgaris Bafverstedt (21b) described a patient who had a specific maculopapular eruption, resembling that of secondary syphilis, which underwent involution following treatment with Perandren® and penicillin However, this type of cutaneous eruption is rarely associated with leukemia One patient described by Bafverstedt had cutaneous lesions which simulated those of scleroderma Lavenson's (372) patient had umbilicated and bullous lesions superimposed on the specific cutaneous nodules

Chronic lymphocytic leukemia associated with nodular or circumscribed cutaneous lesions does not eventuate in the specific picture of exfoliative erythroderma and well defined tumors do not occur in the course of universal or generalized leukemia cutis, according to Arndt (14b) However, several patients who had exfoliative erythroderma, as well as cutaneous nodules, have been described The incidence of nodules following erythroderma was reported by Beek (39a) to be six per cent A patient described by Sweitzer (666) had exfoliative dermatitis as well as flat cutaneous nodules on the nape of the neck Bernhardt (43) reported a patient who had generalized exfoliative dermatitis associated with nodular cutaneous lesions Rosenfeld's (575) patient first presented exfoliative dermatitis followed by cutaneous nodules involving the inguinal regions, under the breasts, the popliteal fossae, gluteal folds and around the umbilicus Splenomegaly occurred simultaneously with the appearance of the cutaneous lesions In the patient reported by Senear (624b), the first manifestation was the cutaneous nodules which were followed by exfoliative dermatitis Keim (333c) described a 68 year old man who had lymphocytic leukemia before exfoliative erythroderma, with numerous nodules superimposed on the

the course of the disease, they usually appear during the so called "aleukemic" phase This designation, in my opinion, does not appear to be justified since, as pointed out by Wiseman (739a), *there is no fundamental pathologic difference* between cases having a low or high total leukocyte count The appearance of cutaneous nodules is usually considered to be a grave prognostic sign, although many patients have had such nodules one to several years before death Three patients having symptomatic cutaneous involvement associated with leukemia were described by Borda and Celani (66) The first was a 70 year old woman whose initial symptoms of chronic lymphocytic leukemia were a small "lymphocyte filled" tumor of the left cheek and the bone marrow picture of lymphocytic leukemia The second patient, a 57 year old woman, had chronic leukemia associated with cutaneous nodules and edema of the face In the third patient, an adult man, the cutaneous involvement of the face simulated mycosis fungoides clinically but the hemogram disclosed 84,000 white *blood cells per cu mm Degos et al (143c) reported a 64* year old man who had various cutaneous lesions There were nodules as well as purpuric lesions within the areas of cutaneous infiltration Histologic study of the infiltrates disclosed marked homogenous proliferation of the lymphocytes and numerous lymphoblasts The diagnosis was "subacute lymphocytic leukemia" There was a remarkably beneficial and rapid' improvement following cortisone therapy

The leukemic tumors may originate as small papular lesions of blue, red, or yellow-brown color, which increase slowly in size and number Single cutaneous nodules occur very rarely, as in the cases described by Barnes and Moffatt (27), Bechet (36b), Gate *et al* (213b), and Zeisler and Caro (750c) A 90 year old man who had cutaneous lesions of 17 months' duration, associated with lymphocytic leukemia, was reported by Degos *et al* (143d) The lesions were infiltrated, papular, and nodular

The nodular lesions are occasionally impossible to differentiate clinically, according to Forkner (192c), because of their

Claus' (114) patient had marked leukemic involvement of the tonsils, uvula, and buccal mucosa Drake (153) described a patient who had bluish black hemorrhagic nodules on the left side of the tonsil

There are some reports of spontaneous regression of the lesions following therapy However, a 71 year old woman who had spontaneous regression of the cutaneous nodules on two occasions, without therapy, was reported by Sjogren (635) This patient had undergone surgery for pyloric carcinoma and, six months later, moderately solid "pinhead to split pea sized, pink colored cutaneous papules developed These lesions were generalized but most pronounced on the extremities There were 20,000 white blood cells per cu mm, with 80 to 90 per cent lymphocytes Histologic study of a cutaneous lesion disclosed a dense infiltration of lymphocytic cells in the dermis The cutaneous lesions receded spontaneously However, five months later the cutaneous picture had changed There were numerous "split pea" sized, purple infiltrations which tended to be of a larger size on the anterior surfaces of the extremities These larger lesions developed central sloughing with a purulent exudate and simulated a pustular syphilitic eruption However, following penicillin therapy, they again regressed A patient reported by Nomland (482) presented cutaneous nodules following roentgenotherapy to the enlarged lymph nodes

A fair representation of the primary sites of involvement is apparent in 93 cases from the literature (Table I)

Other patients who had lymphocytic leukemia associated with cutaneous involvement have been described by Gallasch (208b) Hunter (301), Lavenson (372), Linser (394), Nicolau (479a) Oertel (486), T Oliver (490), Pardee and Zeit (501), Seelig (619), and Shattuck (628) Veasey (696) described a patient who had multiple cutaneous nodules associated with lymphocytic leukemia as well as conductive deafness in both ears due to the leukemic infiltration

Case Report A 59 year old man first presented deeply pigmented cutaneous lesions in the center of the back

dermatitis, appeared One of Wile and Straumfjord's (731g) patients first had exfoliative dermatitis and chronic lymphocytic leukemia Specific cutaneous nodules appeared intermittently on various parts of the body and verrucous and condylomatous lesions involved the ankles They also described a 68 year old man with exfoliative dermatitis whose skin assumed a bluish color, particularly over the extremities, followed by nodules over the upper portion of the trunk

A 59 year old woman in whom the clinical diagnosis of lymphocytic leukemia was made by tissue imprints was reported by Haserick (263) He believed this procedure for diagnosis to be of value when the bone marrow and peripheral blood studies are normal Specific cutaneous involvement by nodules may be definitely established by this procedure He described the technic for this rapid, office procedure test, as follows Tissue from a typical cutaneous induration is removed with a dermatologic punch The fresh, unfixed tissue is then 'blotted' to remove excess blood It is then pressed firmly several times on clean glass slides which are 'fixed" rapidly by drying or with gentle heat to prevent disintegration of the nuclear pattern and then stained with Wright stain, following the usual procedure An imprint from normal skin usually reveals only torn collagenous bundles and a few fixed tissue cells However in leukemia cutis or lymphosarcoma, there are usually an abundance of pathognomonic cells present

The site of predilection for nodular cutaneous lesions appears to be the face In a large series of cases, Beek (39a) found that 64 per cent of these patients had nodules on the head Generalized nodular involvment is infrequent, although patients having this involvement most marked on the trunk, breasts, scrotum, and penis, have been described The mucous membranes are rarely involved by leukemic nodules Although this is a frequent occurrence in lymphosarcoma there are some reports of this involvement with leukemia A patient reported by Shaw and Loughlin (629) had purple colored lesions on the tonsils and a nodule involving the left lingual tonsil

ing a violaceous border, appeared on the right frontal area of the scalp the upper lip, trunk, and the dorsum of the extremities One on the lower part of the back was 10 by 4 cms in diameter He died four months after the first cutaneous involvement appeared and autopsy disclosed numerous elevated, pigmented lesions Those which had been present when radioactive phosphorus was administered had regressed, leaving a brown pigmentation Their surface was flat but many remained elevated, firm and bluish grey in color with a violaceous border Histologic examination of a cutaneous lesion which had not been treated with radio active phosphorus revealed a massive infiltration of small lymphocytes in the dermis which completely filled the subepithelial structures This infiltration penetrated into the adipose layer The diagnosis was lymphocytic leukemic cutaneous infiltration Histologic study of a lesion which had been treated with radio active phosphorus showed collections of lymphocytes in nodules surrounded by a fibrous reaction The diag nosis was cutaneous infiltration due to lymphocytic leukemia The anatomical diagnoses were chronic lymphocytic leukemia and lymphocytic leukemic in filtration of the liver, skin kidneys, lung lymph nodes spleen and bone marrow

Case Report A 30 year old man presented small, slightly tender cutaneous nodules, of normal "skin color," over the back and shoulders They had first ap peared one month ago [illegible]

the groin axilla and scalp Simultaneously, weakness, fatigue, shortness of breath, and a heavy feeling in the abdomen appeared, together with bleeding from the gums On examination the mucous membranes were pale and there were numerous bluish red, 5 to 25 mm cutaneous nodules involving the upper part of the

TABLE I
SITES OF INVOLVEMENT OF CUTANEOUS NODULES

Site of Involvement	*Per Cent*	*Number of Cases*	*Total Cases*
HEAD AND NECK			
Cheeks and forehead	23 62	23	
Nose	7 52	7	
Eyelids	6 45	6	
Eyebrows	6 45	6	
Ears	5 37	5	
Lips	1 07	1	
Chin	1 07	1	
Scalp	4 30	4	
			53
TRUNK			
Trunk	3 22	3	
Breast	15 0	14	
			17
EXTREMITIES			
Hands	1 07	1	
			1
MUCOUS MEMBRANES			
Tonsil	3 22	3	
			3
GENERALIZED	20 43	19	
			19
			93

of three month's duration Two months later another appeared on the back adjacent to the initial lesion They increased rapidly in size and became tender to palpation Similar lesions had been present on the scalp and lower lip for one week when others appeared on the extremities and anterior and posterior surfaces of the trunk Histologic examination of these lesions revealed "lymphoblastoma, *probably mycosis fungoides* group," and that of a tumor in the nasal soft palate showed "lymphoblastoma" The lesions regressed markedly following therapy with radioactive phosphorus Slightly elevated, 1 5 to 2 cm, bluish-grey lesions, hav-



Figure 17 Cutaneous ecchymoses of head, thorax and extremities (case report)

and extremities Enlargement of all lymphoid tissues of the body, in close approximation to the peripheral blood vessels, became nearly generalized There were 528,000 peripheral white blood cells per cu mm He died four months after the first symptoms had occurred At autopsy the skin was dry and "blotched," with purpuric lesions most marked on the face and neck The skin of the face was of a deep purple color, except for a few normal skin colored areas around the nose, mouth and ears The skin and subcutaneous tissues of the anterior portion of the neck were indurated as a result of subcutaneous hemorrhages The purpuric lesions on the anterior surface of the lower legs consisted of oval or circular, 1 to 5 cm nodules, some with purple centers There was purpura of the mucous membranes within the oral cavity The anatomic and histologic diagnoses were lymphocytic leukemia with purpura

back, shoulders and scalp There was generalized lymphadenopathy and hepatosplenomegaly The hemogram, as well as histologic examinations of a lymph node and an intracutaneous nodule, disclosed acute lymphocytic leukemia Two months after the appearance of the first symptoms he had generalized alopecia, as well as bluish, elastic nodules involving the sternum and, more extensively, the trunk and there was one large nodule on the anterior area of the scalp The left hand was swollen and there was pitting edema of the ankle Hemogram disclosed 72,000 white blood cells per cu mm He died eight months after the onset of the disease The anatomical diagnoses at autopsy were chronic lymphocytic leukemia, empyema of the left lung, bilateral bronchopneumonia, and emaciation Histologic examination revealed leukemic infiltration of the skin, lymph nodes, and adrenal glands

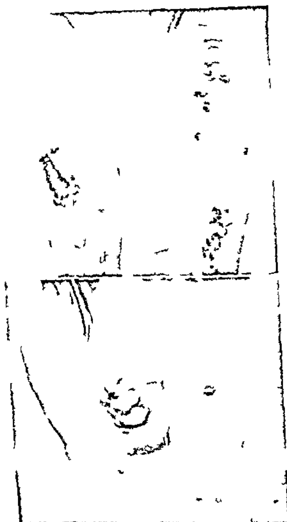
Case Report A 27 year old man first noted fatigue and shortness of breath three months' previously followed, two months later, by the appearance of red cutaneous macules on the legs and on the temporal side of both eyes He had pain in the upper left region of the abdomen for the previous two weeks and hemorrhages in the lips gums, and buccal mucous membranes for the last four days On examination, the lips and throat were dry, the face was swollen over the malar region, and there were fading hemorrhages on the eyelids, arms, and lower legs There were extensive bilateral subconjunctival hemorrhages The lips were pale in color, slightly swollen, and there was purpura on the upper lip There were several hemorrhages of the gums, which were soft and pliable, and a large bloody extravasation of the posterior palate, as well as a small ulcerated lesion on the tip of the tongue Two weeks later he had marked swelling of the face, lips, and neck, difficulty in breathing and cutaneous ecchymoses, which increased in severity, on the head, thorax

soles, and scalp These plaques were of a purple color, hemorrhagic, slightly elevated, thick, and firm The mucous membranes of the mouth and conjunctivae were similarly involved and superficial ulceration with secondary infection and crusting, was most marked in these areas

Case Report A 27 year old man first noted a gradual loss of weight four months previously He had increasingly severe dyspnea for seven weeks and left cervical lymphadenopathy for "several" weeks A diagnosis of leukemia (acute blast form) and secondary anemia was made and he was given transfusions of whole blood On examination, he had discrete, 1 cm, nontender, freely movable enlarged lymph nodes which were generalized and also involved the epitrochlear region The spleen was palpable 4 cms, and the liver 3 cms below their costal margins There were petechiae in the mouth and a purpuric cutaneous eruption of minute, reddish purple lesions involving both feet and ankles, most marked over the dorsum of the feet At the first examination the hemogram revealed 8 5 gm hemoglobin 2 680 000 red blood cells and 98 000 white blood cells per cu mm Preceding death one month later, there were 11 gm hemoglobin, 3 100,000 red blood cells and 23 000 white blood cells per cu mm, with 1 per cent segmented cells and 99 per cent lymphocytes The sedimentation rate was 27 mm in one hour and the hematocrit 25 per cent He was given roentgenotherapy, transfusions of whole blood, urethane and general supportive therapy, but his condition did not improve He became weaker and the lymphadenopathy and splenomegaly became more marked Cutaneous infiltrations then occurred and the purpura increased in severity The clinical diagnosis was "subacute" lymphocytic leukemia At autopsy, the skin and mucous membranes were pale, yellow in color, moist, edematous and smooth, and markedly crepitant There was marked enlargement of the neck from subcutane-

2 *Infiltrations or Plaques.* Infiltrated or plaque like lesions are not a frequent specific cutaneous manifestation of lympho cytic leukemia As in the nodular form, the face appears to be the site of predilection for these lesions Pelagatti's (515b) patient had leukemic infiltration of the scalp which simulated cutis verticus gyrata A 65 year old man, who had rapidly progressive thickening and grooving of the scalp for four months, was reported by Popow (536) Leder (376) described a 58 year old man who had cutaneous leukemic infiltrates involving the eyebrows, nose, cheeks, and ears A 64 year old man who presented several pink infiltrations, 2 5 cms in size, on the forehead and diffuse infiltration of the cheeks, was reported by Andrews (10a) A 74 year old man who had bluish infiltrations on the face and trunk was described by Milbradt (447 case 1) Cutaneous infiltration of the extremities was reported by Barney (28d) in a patient who had involvement of the anterior surface of the tibia These lesions resembled localized myxedema A patient who had "patchy, paste-like cutaneous infiltrations of the right thigh was described by Matras (438) A 35 year old woman, reported by Bechet (36a), had infiltrated, copper red very sharply defined cutaneous plaques involving the areola of both breasts

Generalized involvement with cutaneous plaques or infiltrations appears to be very infrequent in lymphocytic leukemia A patient reported by Leviseur (386) first presented cutaneous erythema, scaling and pruritus which clinically resembled mycosis fungoides However the hemogram indicated leukemia Infiltrated patches then appeared on the forehead and later there were fungating tumors which showed diffuse erythematous infiltration, particularly around the eyebrows and extending well into the scalp There were granulomatous nodules on the chin and small nodules ulcerations and abrasions over the buttocks Blankenhorn and Goldblatt (52) described a man who had infiltrated cutaneous lesions, "from miliary points to patches more than 5 cms in diameter,' involving the entire cutaneous surface, including the palms,



F gure 18 Ulcerat on of tl e leg (*A M A Arch Dermat* 73 189 1956)

F gure 19 Ulcernnon of chest wall from an underlying lymph node (*A M A Arch Dermat* 73 189 1956)

ous emphysema A black, firm, disc-shaped intracutaneous lesion was present on the right side of the upper lip The eyelids and conjunctivae were "puffy" and crepitant There was generalized lymphadenopathy Numerous leukemic infiltrates were scattered over the skin and mucous membranes but were most marked on the mucous membranes inside the cheek, skin of the neck, abdomen, and lower extremities, particularly on the dorsal aspects of the feet Histologic examination revealed leukemic infiltration of the lungs, liver, lymph nodes, and skin The anatomic diagnoses were subacute lymphocytic leukemia, bilateral bronchial pneumonia, and subcutaneous emphysema

3 *Ulcerated Lesions.* The cutaneous nodules which are associated with leukemia seldom become ulcerated Beek (39a) found the incidence of leukemic ulceration to be 8 per cent This ulceration is usually the result of infection or trauma The majority of reports of ulcerated lesions appear to indicate that the extremities are the sites of predilection

Sirota and Kusnetz (634) reported a 31 year old man whose first symptom was the occurrence of several necrotic ulcers, mainly on the lower extremities, which showed, on histologic examination, a dense collection of immature lymphocytes at the base of the ulcerations and in surrounding tissues Four months later lymphadenopathy, splenomegaly, and peripheral blood changes typical of lymphocytic leukemia appeared He also had ulcerated lesions in the throat during the acute phase of the disease Hedges (270) patient was a 51 year old man who presented a small ulcer, with undermined edges, along the lymphatic vessels of the right arm Ulcerated nodules subsequently occurred on the legs trunk and scalp The clinical picture in this case resembled that of tularemia or sporotrichosis A 56 year old man who first had small ulcers, which had thickened borders, on the knuckles and backs of the hands with ulceration of the tip of the left pinna was reported by Semon (623) Seven years later a superficial membranous deposit had developed on the soft palate and uvula

The patient described by T Oliver (490) had an oval-shaped tumor in the axilla which was complicated by cutaneous necrosis A patient who had cutaneous nodules involving the face, which became ulcerated, was reported by Felsenbrunn (183) A 68 year old man who had chronic lymphocytic leukemia for five years and cutaneous ulcerations on the left buttock and right thigh for two and one-half years, was described by Cannon (97b) Although roentgenotherapy appeared to "heal" the ulcer on the thigh, large ulcerations subsequently occurred over the right sacral area and buttock. The skin in these areas was infiltrated, shiny and of a purplish color There were two ulcers in this area one was red with flat granulations and was lined by thick edematous skin with over hanging edges, while the other ulcer was mostly overgrown by finger like granulation tissue

Another uncommon manifestation is cutaneous ulceration of the genitalia with a clinical picture simulating that of primary syphilis or other venereal diseases Three patients having this involvement were reported by Bluefarb and Webster (56m) The first patient was a 35 year old Negro who was known to have had chronic lymphocytic leukemia for two years On examination he had two lesions on the ventral surface of the penis which had been present for 10 days These 2 by 3 cm cutaneous lesions were red, raised and granulomatous He had marked bilateral inguinal lymphadenopathy The hemogram disclosed 26 per cent hemoglobin, 1,610,000 red blood cells and 141,000 white blood cells per cu mm, with 94 per cent lymphocytes Histologic study of the larger lesion showed changes of lymphocytic leukemia cutis The second patient, a 64 year old Negress, was known to have had chronic lymphocytic leukemia for 12 years She presented a 4 by 4 cm granulomatous lesion on the vulva and two smaller granulating lesions at the perineal raphe These lesions were of a bright red color and nodular She had inguinal lymphadenopathy Histologic examination of the lesion on the vulva showed changes of lymphocytic leukemia The third patient was a 35 year old Negress who had chronic lymphocytic leu

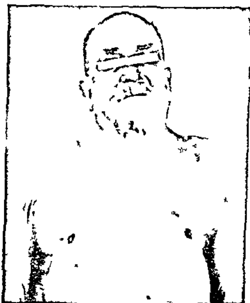


Figure 20 Marked lymphadenopathy with ulcerated nodule of left shoulder



Figure 21 Ulcerated nodule of the upper lip
Figure 22 Close up of Figure 21

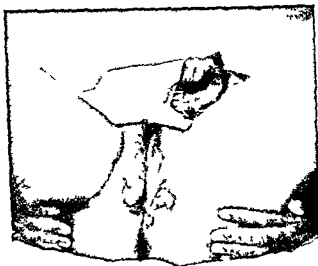


Figure 25 Ulcerated nodular lesions of lymphocytic leukemia on the genitalia (*Quart Bull Northwestern Univ M School* 27 18 1953)



Figure 26 Ulcerated nodular lesions of lymphocytic leukemia on the genitalia



Figure 23 Ulcerated nodular lesions of lymphocytic leukemia on the genitalia (*Quart Bull Northwestern Univ M School* 27 18 1953)



Figure 24 Ulcerated nodular lesions of lymphocytic leukemia on the genitalia (*Quart Bull Northwestern Univ M School* 27 18 1953)

kemia She had cutaneous lesions on the vulva and perineal raphe which were found to be lymphocytic leukemia cutis on histologic examination I have recently observed another Negro patient who had a leukemic ulcer of the penis

Two patients described by Baldridge and Awe (25a) had ulcers on the penis Primary syphilis was suspected to be present in both cases but darkfield studies were negative for treponema pallidum However histologic examinations showed the characteristic picture of lymphocytic leukemia A 37 year old man reported by Shaw and Loughlin (629) presented leonine facies shallow cutaneous ulcerations in the sacral region and a small ulcer on the penis Keim s (113) patient was a 47 year old woman who presented a small ulcer on the left labia majora which was similar to other ulcers involving the left axilla and left thigh Both the hemogram and histologic studies of the lesions showed the typical picture of lymphocy

lymph nodes the spleen liver lungs and skin of the face

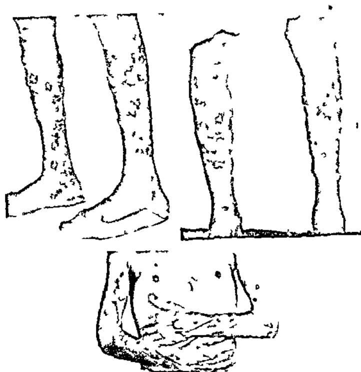
Case Report A 55 year old man with chronic lymphocytic leukemia had small cutaneous lesions which had appeared suddenly around the lips and nose 10 days previously There was slight bleeding from the lesion on the nose On examination, there was a crusted lesion in the left nostril and several cutaneous lesions on the lips There were numerous soft nontender discrete freely movable enlarged cervical lymph nodes most marked on the left side The spleen was palpable 11 cms and the liver 2 cms below their costal margins There was marked inguinal lymphadenopathy Two months later he had impetiginized cutaneous lesions on the upper lip and chin and a 2 cm yellowish crusted lesion in the bearded area These lesions had not improved following treatment with 2 per cent ammoniated mercury ointment or with local application intramuscular injection or parenteral administration of penicillin Two weeks later he had an ecchymotic cutaneous lesion on the left side of the nose which involved the left ali nasi There were heavily coated dark crusts and ulcerations covering the face He died two and one half months after the cutaneous lesions first appeared on the face At autopsy the diagnoses including histologic findings were chronic lymphocytic leukemia generalized lymphadenopathy generalized petechial hemorrhages leukemic infiltration and hemorrhage of the lungs hepatomegaly and leukemic infiltration of the liver petechiae and leukemic infiltration of the kidneys and ulcerative lesions of the skin and perioral regions

4 *Leukemic Erythroderma* (Discussed in Chapter VII)

5 *Other Cutaneous Lesions* Although the most frequent specific cutaneous lesions which occur in lymphocytic leukemia are of the nodular infiltrative ulcerative or erythroderma type other cutaneous eruptions which cannot be classified in

tic leukemia. A patient described by Traub (688b) had an ulcerated lesion on the labia majora which showed leukemic infiltration of the dermis on histologic examination

Case Report. A 56 year old man had cervical lymphadenopathy which had developed suddenly one and one-half years' previously. A diagnosis of lymphocytic leukemia was made at that time He was given roentgenotherapy. On examination, there was generalized lymphadenopathy and the liver was palpable 8 cms below the costal margin The hemogram revealed 128,000 white blood cells per cu mm, with 5 per cent segmented cells, 88 per cent lymphocytes, 6 per cent eosinophils, and 1 per cent monocytes Roentgenogram of the chest disclosed widening of the the hilar shadow with numerous calcifications and increased linear markings radiating from the hilus There was some infiltration in the first anterior interspace, bilaterally, particularly on the right side and at the right base Two months later, crusted, red cutaneous lesions had appeared over the entire lip and extending into the nostrils, and the tip of the nose was red and tender There were a few papulo-vesicular cutaneous lesions on the cheeks, chin, left wrist, and the dorsum of the right hand He had generalized lymphadenopathy and marked splenomegaly Histologic examination of the cutaneous lesions revealed "leukemia cutis," and that of a lymph node "leukemic transformation" He was given penicillin, roentgen ray, and topical therapy and all of the cutaneous lesions disappeared However, nine months later he had a recurrence of the cutaneous lesions on the nose, right hand, left wrist, and around the mouth *These lesions were extremely painful and* increased in severity despite therapy He died several days later and the diagnoses, at autopsy, were lobar pneumonia of the right lower lobe and chronic lymphocytic leukemia with leukemic infiltration into all



Figures 27 28 and 29 Rupia like nodular lesions

65 year old man who had a diffuse papulo nodular cutaneous eruption involving the inner middle one-third of the right leg and to a lesser degree the backs and sides of the legs The nodules were soft of "medium size and tended to group in small clusters in some areas The cutaneous picture resembled that of hypertrophic lichen planus F T Becker (37b) described a 78 year old man who first presented edema of both hands forearms feet and ears simulating the edema which occurs in lymphangioma There were hard pea" sized movable nodules in the swollen areas of both hands and ears Histologic study revealed accumulations of pro lymphocytes around the lymphatic vessels which were be

these groups are occasionally encountered

Koch (347) described two women, aged 59 and 54 years respectively, who presented juxta-articular nodes on the elbows and forearms during the course of lymphocytic leukemia

Several patients who had cutaneous lesions simulating lupus erythematosus have been described Therefore, it has been suggested that lupus erythematosus (as well as rosacea) be considered in the differential diagnosis of leukemia cutis A 76 year old man, described by Haxthausen (265), had several raised patches of dermatitis on the face, most marked on the cheeks and around the nose and eyes There was a marked similarity to "butterfly" lupus erythematosus but histologic study revealed leukemia Feit's (182a) patient had yellow red papules, some densely set, that formed a 2 5 cm lesion which infiltrated in a "bat-like" manner to the adjacent parts of the cheeks and simulated lupus erythematosus This patient also had bluish-red infiltration, studded with small nodules, involving almost the entire scalp Neuberger (474) reported a 61 year old man who first had a "red spot" on the right cheek two years previously and eight months later a similar lesion appeared on the left cheek A diagnosis of lupus erythematosus was made On examination, two years after onset of the first lesion, there were lobulated, painless tumors on both cheeks Histologic study of a cutaneous lesion and a lymph node revealed lymphocytic leukemia The cutaneous lesions which occurred in Schildkraut's (604) patient resembled rosacea and involved the "butterfly" area of the face

Other cutaneous lesions associated with lymphocytic leukemia have been described as resembling rupia, hypertrophic lichen planus, lymphangioma, localized erythroderma and pityriasis lichenoides

The 58 year old man reported by Bertaccini (44b), presented slightly elevated, circular, crusted, dark brown cutaneous lesions, which simulated rupia, on all extremities Histologically, the cutaneous lesions were densely infiltrated by lymphocytes, they were necrotic and, in some areas, the surface was ulcerated MacKenna and Davie (418) reported a

IV

GRANULOCYTIC LEUKEMIA

A. History

THE CUTANEOUS manifestations associated with granulocytic leukemia were described at a much later date than those which occur with lymphocytic leukemia One of the first recorded cases of this association was that of Winiwarter (736) in 1892 followed by the reports of Hindenberg (283) in 1895, Hirschlaff (286) in 1895, and two cases described by Nekam (271) in 1899 The patient described by Winiwarter was a 19 year old boy who had red tumors on the trunk, chest and abdomen A 40 year old woman who had a 6 cm tumor on the thigh for one year was reported by Hindenberg The first patient described by Nekam was a 30 year old man who presented generalized pruritus and macular cutaneous lesions on the abdomen and legs which subsequently became papular His second patient was a 37 year old woman who presented bluish red maculo papular lesions on the abdomen

B. Etiology

Cutaneous lesions do not occur as frequently in granulocytic leukemia as in lymphocytic leukemia However, when these lesions do occur in granulocytic leukemia, they are as characteristic of the disease as those present in Hodgkin's disease or lymphosarcoma, according to E. Epstein and MacEachern (166) They found specific cutaneous lesions to be present in 5 5 per cent of their cases of granulocytic leukemia

lieved to have obstructed the lymphatic flow, thus producing the lymphedema A 33 year old man who had chronic lymphocytic leukemia for six years was described by Rothman and Felsher (583) Symmetrical erythema had been present on the cheeks and in the parietal, temporal and postauricular regions for one year A few weeks after onset of the erythema, slight infiltration occurred in the postauricular regions The clinical picture was thought to resemble localized erythroderma. The patient reported by Norman (484) was a 42 year old man who had "fairly thick," slightly raised, small brown cutaneous papules, some of which were hemorrhagic The lesions simulated those of pityriasis lichenoides There was also cutaneous infiltration, of a bluish color, involving the back Histologic examination of the small cutaneous lesions revealed leukemic infiltration

ed potentially granulopoietic tissue is apparently located be- [illegible] ...dventitial histiocytes about the smaller blood [illegible] The his[illegible] hemocy[illegible]toblasts However, [illegible] fibrocytes may transform into granulocytic cells in leukemia Piney (524a) believed that myeloid tissue is normally not present outside the bone marrow (no subcutaneous myeloid structures comparable with the "lymphomata" of Ribbert) and cutaneous infiltrations associated with granulocytic leukemia are therefore, always metastatic He believed this conclusion to be logical when the immaturity of many of the circulating blood cells is considered They are therefore capable of reproduction and also their presence in the blood stream is an excellent situation for producing embolism Piney also be[illegible] ...taneous in[illegible] ...med by the fact that the circulating blood cells are [illegible] ture in this form of leukemia and are, therefore more capable of proliferation

The cases studied by Barney (28b), Hudelo *et al* (299) and by Ketron and Gay (338b), among others, all favor the theory [illegible] since practically [illegible] Arzt's (16c) case the lymphoid tissue was completely replaced by myeloid tissue, indicating an independent proliferation rather than a simple infiltration Bruusgaard (81) observed nearly complete destruction of elastic fibers produced by a very dense infiltration of megakaryocytes myeloblasts, and eosinophils such as occurred in the patients reported by Pelagatti (515a) and Sannicandro (596i) In these two cases the marked increase of mitoses was a prominent feature

Rohr (571) theorized that extramedullary foci are present in the spleen and liver of patients having leukemia, from which foci of myelocytic cells metastasize in the skin by way of the blood and lymph vessels prior to the occurrence of

The cutaneous lesions occasionally precede other symptoms of leukemia, as in the 16 year old girl described by Beek and Wyers (39b)

The important difference between the cutaneous manifestations of the acute and chronic forms of granulocytic leukemia, according to Nekam, Jr (472b), is that tumors practically never occur in the acute form but they constitute a characteristic clinical picture in the chronic form of the disease

1 *Age and Sex Incidence.* Among 47 reported cases having sufficient data for tabulation, the following age incidence was found

Age, Years	*Men*	*Women*
Birth to 9	2	0
10 to 19	4	3
20 to 29	3	3
30 to 39	8	1
40 to 49	3	6
50 to 59	3	4
60 to 69	4	2
70 to 79	1	0

There were 28 (60 per cent) men, in whom the average age at onset of the disease was 37 years, and 19 (40 per cent) women in whom the age at onset was 40 21 years

Nekam Jr (472b) was unable to draw any conclusions regarding the pathogenesis of granulocytic leukemia In the majority of cases he studied the histologic study revealed only perivascular infiltrates of variable density composed of granulocytic cells Jaffe (314c), who studied the inflammatory defense reactions in leukemia found that, even in a diffusely lymphocytic bone marrow the granulocytic cells can proliferate and encroach on the lymphatic tissue when stimulated by infection If granulopoiesis is completely exhausted there is no defense reaction against infection Although it is generally agreed that the granulocytic cells of an exudate are derived from the blood, extramedullary granulopoiesis occurs which, in some cases, may result from colonization of immature bone marrow cells However, in the majority of cases, the cells are produced locally In the normal organism, the undifferentiat

C. Cutaneous Lesions

Specific cutaneous lesions may occur in the course of granulocytic leukemia or its "aleukemic" form The typical nodular [illegible] in- [illegible] and [illegible] ary-ing from "pinhead" to "cherry" size and their color ranges from that of normal skin to deep purple The cutaneous nodules associated with lymphocytic leukemia have a predilection for the face, while the nodules occurring with granulocytic leukemia primarily involve the trunk The face, scalp and extremities are rarely affected and local symptoms usually do not occur

Barney (28b) described the specific cutaneous lesions associated with granulocytic leukemia as "pinhead to walnut" sized, firm, sharply circumscribed, brown or bluish colored, asymptomatic nodules which chiefly involve the trunk and, less frequently, the face, scalp and extremities The nodules are either raised above the surrounding skin, to which it is intimately attached, or occur in deeper portions of the subcutis They occasionally become confluent, forming larger plaques In a few cases the nodules become ulcerated with purulent degeneration, crusting, scaling, hemorrhage and telangiectases

A patient described by Almkvist and Arzt (5) presented a nodule on the lower lip which had a clinical resemblance to a chancre Herxheimer's (278b) patient had "pinhead to nickel sized" nodular lesions on the body and a "fist" sized tumor on the nape of the neck Oral mucous membrane involvement is occasionally described, but only in the cases reported by Almkvist and Arzt (5) and Arzt (16a) was the specific character of the lesions established by histologic examination Barney (28b) found that pruritus and pain were infrequent symptoms and the number of lesions varied from one, as reported by Gans (210a), to almost universal involvement, as described by Ketron and Gay (338b) The patient

peripheral blood changes of leukemia This theory of pathogenesis was supported by the reports of Herzberg and Schuppener (279) who gave detailed clinical and histologic reports of two patients who presented specific cutaneous lesions preceding the peripheral blood changes of leukemia

Histologic examination of the cutaneous nodules usually reveals flattening of the rete pegs over the infiltrate in the epidermis The bulk of the infiltrate is in the corium and upper layers of the subcutaneous tissue, grouped mainly around the cutaneous appendages The infiltrate may penetrate into the fatty tissue as described by Rolleston and Fox (572b) and Saphier and Seyderhelm (597) The infiltrate is usually polymorphous in chronic granulocytic leukemia, a feature not usually present in the acute form of granulocytic leukemia or in lymphocytic leukemia Practically all cells of the granulocytic series may be found in the infiltrate polymorphonuclears, eosinophils, basophils, myelocytes, myeloblasts and, occasionally, histiocytes, mast cells, lymphocytes, plasmacytes and monocytes



Figure 30 Typical leonine facies due to leukemic nodules (Courtesy of William Ford, M D, Univ of Illinois, College of Medicine)

the tumors However, Hirschlaff (286) and Schleip and Hildebrandt (606) described the lesions as "brilliant white," Hartmann (261) as "flesh colored," Kerl (337) as "green" De Langen (145) as "greyish violet," Lubliner (402) as "reddish brown" Lutz (407) as "dull yellow," and Steinbrinck and Stukowski (649) as "yellowish brown" The yellow color of the lesions was stressed by Nekam, Jr (472b) who noted that the tumors frequently have a clear central zone, while the periphery is surrounded by a red halo

The trunk is most frequently involved by cutaneous lesions, while the extremities are the next most frequent sites of involvement A predilection for the face does not occur in granulocytic leukemia as it does in lymphocytic leukemia However patients having cutaneous nodules involving the face have been described by Almkvist and Arzt (5), De Langen (145), Hartmann (261), Hudelo *et al* (299), Tennenbaum (677) Lutz (407), and Saphier and Seyderhelm (597) The *patient reported by Walther and Strocka (706) had a rosacea*-like exanthem which was histologically specific of leukemia

The cutaneous lesions do not usually ulcerate but there is a tendency toward ulceration when the mucous membranes are involved De Langen (145) and Saphier and Seyderhelm (597) described central necrosis of leukemic nodules Spontaneous regression of the lesions was mentioned by Hollander *et al* (292)

Ketron and Gay (338b) reported a 62 year old woman who had been ill for two years She had "pinhead to pea" sized, bluish red, slightly elevated intensely pruritic cutaneous lesions, which resembled urticaria, involving the costal margins of the abdomen These lesions increased rapidly in size and, within a few days nodules had [illegible]
and behind the ears [illegible]
slight lymphadenopathy [illegible]
spells" were her major symptoms The cutaneous eruption became generalized two months later and the nodules had greatly enlarged in size some being 2 or 3 cms in diameter There was nearly complete closure of the right ear canal by

reported by Gans had polycythemia and a deeply infiltrated "mass" involving the left hip which was histologically specific but there was an aleukemic myelosis The cutaneous lesions preceded the leukemic peripheral blood changes in Ketron and Gay s patient and they considered this early stage to be an "aleukemic' myelosis

"Aleukemia' was present in Arzt's (16b) patient, who had specific cutaneous lesions involving the trunk, and also in Herxheimer's (278b) patient who had a nodular cutaneous eruption on the trunk A 45 year old man, reported by E F Zimmermann and Curtis (753) had "millet seed to quarter" sized cutaneous nodules which were pinkish grey and copper to a purplish hemorrhagic color, involving the trunk and all extremities These lesions were painless, freely movable, and appeared to be attached to the skin and subcutaneous tissues The gums were tender and bled easily, while small petechiae were present on the left tonsillar pillar A case of diffuse nodular aleukemic' granulocytic leukemia was reported by Baldridge and Fowler (25b) This patient, a 22 year old woman first had pain and swelling of the knees, fingers, wrists, and elbows followed, three months later, by small white nodules on the face and neck Subsequently, similar nodules appeared on the entire body, particularly on the forearms and legs and numerous firm 0 5 to 1 cm nodules involved both breasts A 77 year old man who first noted bluish patches on the legs two years previously was described by Roxburgh and Russell (587) These lesions gradually spread upwards and finally involved the face He had indurated papules over most of the body and on the face which became raised to form tumors, producing a leonine facies

There are varied descriptions of these cutaneous nodules Nekam, Jr (472b) stated that they were "generally firm and elastic in consistency,' Lubliner (402) described them as "cartilaginous" and Whitehouse (729b) and Richter (559b) as "very soft " The color of the lesions, usually described as livid red or blue, Whitehouse believed might be due to telangiectasia or hemorrhages and extravasated blood into

in the cutis The majority of cells in the infiltrate were granulocytic leukemic cells consisting of neutrophilic myelocytes basophilic myelocytes eosinophils and large lymphocytic cells She died 11 days after the cutaneous lesions appeared and the diagnosis of granulocytic leukemia was confirmed at autopsy

Buschke and Hirschfeld (87b) reported a 22 year old woman who presented generalized "cherry to plum" sized cutaneous nodules The hemogram was "normal but aspiration of a cutaneous nodule revealed large "atypical" lymphocytes and monocytes Four and one half months later there were 33 000 white blood cells per cu mm which consisted almost entirely of "atypical large" lymphocytes She died five and one half months after the appearance of the cutaneous lesions At autopsy there were "tumor deposits" in the bone marrow mesenteric lymph nodes gastric mucosa of the stomach intestine ovaries parametrium and dura mater Histologic examination of a cutaneous nodule and of the internal organs showed infiltration of "atypical large cells" This case was reported as one of "lymphosarcomatosis cutis" but Herxheimer (278b) interpreted it as one of granulocytic leukemia

Arzt s (16a) patient was a 50 year old man who had been ill for three years There were generalized pale or brownish red from "cherry to nut" size cutaneous nodules He had hepatosplenomegaly and lymphadenopathy There were 269 000 peripheral white blood cells per cu mm with 8 per cent myeloblasts and 22 per cent myelocytes Histologic examination revealed a marked infiltration of myelocytes myeloblasts and reticulum cells in the cutis He died two months after the cutaneous involvement appeared and autopsy confirmed the diagnosis of granulocytic leukemia Another patient reported by Arzt (16b) was a 20 year old woman had been ill for three and one half months She had numerous bluish grey "pea to bean" sized cutaneous macules and papules distributed over the trunk, most marked on the breasts She had lymphadenopathy and hepatomegaly There were 5 200 peripheral white blood cells per cu mm., with 90 per cent granulocytic cells She died one month after the

shiny, elastic, mahogany colored, confluent nodules which were sensitive to pressure Numerous nodules, similar to the cutaneous lesions, caused enlargement of the tonsils and numerous nodules and petechiae involved the mucosa of the pharynx. The hemogram ranged from 3,180 to 68,740 white blood cells per cu mm, with from 50 to 92 5 per cent granulocytes and there was a secondary anemia She died four months after the onset of the cutaneous lesions and one month following the peripheral blood changes The diagnosis of granulocytic luekemia was confirmed at autopsy

A 60 year old man, described by Herxheimer (278a), had numerous cutaneous nodules, of "pinhead to baby's fist" size, involving the trunk and nape of the neck He had hepatosplenomegaly and the hemogram ranged from 7,300 to 71,000 white blood cells per cu mm, with 60 to 70 per cent polymorphonuclears and 2 to 3 per cent eosinophils Histologic examination of the cutaneous nodules revealed granulocytic cells The diagnosis of granulocytic leukemia was confirmed at autopsy

The 47 year old woman, reported by Saphier and Seyderhelm (597), had been given roentgenotherapy for leukemia which resulted in "improvement" in the peripheral blood picture and decrease in hepatosplenomegaly However, one year after treatment, "pea to bean" sized, reddish cutaneous and subcutaneous lesions developed on the tip of the nose and ramus of the jaw The lower lip was swollen and infiltrated and hard, red, painless, "lentil to pea" sized nodules appeared on the forehead Two weeks before the appearance of the cutaneous lesions the hemogram revealed 280 000 white blood cells per cu mm, with 16 per cent polymorphonuclears, 58 per cent myeloblasts, 15 per cent eosinophils 8 per cent basophils and 3 per cent lymphocytes On the day of death there were 17,600 white blood cells per cu mm, with 69 per cent myelocytes and myeloblasts Histologic examination of a cutaneous nodule from the nose revealed a cellular infiltration which was most marked in the subcutaneous tissues but was also present around the hair follicles and sweat glands



Figure 31 Nodule of granulocytic leukemia in the deep cutis (A M A *Arch Dermat* 73 189 1956)

The upper lip was so grossly swollen that it overlapped the lower lip There were numerous firm red 1 to 3 cm, elevated nodules on the trunk which were painless and freely movable The hard palate was extensively ulcerated with a foul greyish, easily removable membranous slough and there was severe gingivitis He had lymphadenopathy in the posterior cervical left supraclavicular and axillary regions as well as hepato splenomegaly This patient was later reported by Paul and Limarzi (508) when he presented several indurated elevated cutaneous nodules on the scalp There was edema of the up per eyelids and a marked reduction of the palpebral fissure The swelling of the upper lip projected over the upper teeth and extended upward to involve the nose and maxillary re gion Numerous red to pink indurated elevated freely mov able 1 to 2 cm cutaneous lesions were distributed over the scalp face neck trunk, arms and thighs but were most numerous on the back and chest Histologic examination of the skin revealed dense cellular infiltrations of the co rium and subcutaneous tissue which were most extensive in the subcutaneous tissue The cells formed dense confluent

cutaneous involvement appeared Histologic examination of the skin revealed infiltration of the hypoderm with what appeared to be normal lymphocytic cells The oxidase reaction was positive A diagnosis of granulocytic leukemia was confirmed at autopsy

The patient described by Gottron (238a) had intensely pruritic excoriated cutaneous nodules on the face and neck and a 2 cm nodular leukemic infiltration on the forearm The floor of the mouth was necrotic Histologic examination of a cutaneous nodule revealed an infiltration of myeloblasts The patient died two weeks later and autopsy confirmed the diagnosis of granulocytic leukemia Nekam Jr's (472a) patient was a 62 year old woman who had been ill for 15 days Numerous bluish, brown and pale yellow, 'pea to bean" sized, firm cutaneous nodules had first appeared on the breasts and thighs, while the arms and legs subsequently became involved There was hepatosplenomegaly and the peripheral blood count first showed 21,000 white blood cells per cu mm, but later this count was 2,200 per cu mm with 94 per cent myeloblasts The diagnosis of granulocytic leukemia was confirmed at autopsy Patrassi (507) described a 51 year old man who had acute granulocytic leukemia with cutaneous tumors Detailed peripheral blood studies were recorded during the following two years At autopsy, there were metastatic tumors involving practically all lymph nodes and internal organs, including the heart muscle Yamazaki and Nakano (747) reported a 12 year old boy in whom a tumor of the scalp appeared seven months after an injury He had cervical and retroauricular lymphadenopathy and the hemogram first showed anemia and leukopenia but later revealed leukocytosis Autopsy disclosed granulocytic leukemia involving the bone marrow, lymph nodes and spleen

Senear (624a) reported a 44 year old man who first had nodules on the trunk and, a short time later, on the face, while the lips, particularly the upper, became enlarged There was a typical leonine facies with numerous large, firm, red cutaneous nodules, most prominent in the supraorbital region

occurs mostly from the local cutaneous lesions rather than from the bone marrow or from the blood stream

Ulrich and Parks (693) described a 45 year old woman whose major symptom was "weakness" She had splenomegaly and 180 000 peripheral white blood cells per cu mm with 58 per cent myelocytes and metamyelocytes A diagnosis of chronic granulocytic leukemia was made and she had temporary improvement following roentgenotherapy However ten months later she presented discrete slightly elevated 8 mm cutaneous lesions which had a central yellow area about 3 mms in diameter over both arms and legs Both legs were edematous The lesions healed leaving pigmentation following treatment with roentgen rays and Fowler's solution Autopsy disclosed granulocytic leukemia as well as miliary tuberculosis

A 47 year old woman described by E. C Jones (319) presented a widespread nodular infiltrated cutaneous eruption She had generalized lymphadenopathy and following a sore throat and bleeding from the gums hepatosplenomegaly developed The peripheral blood picture was that of granulocytic leukemia with numerous circulating blast cells A three and one half year old boy described by Gunewardene (247) had "more than a dozen pale 3 75 cm cutaneous nodules on the scalp three months after an attack of measles Simultaneously the peripheral blood picture changed from "secondary anemia to granulocytic leukemia" The cutaneous nodules increased in size and number and spread to involve the forehead and eyebrows However many of these nodules disappeared or decreased in size just before his death Histologically these nodules showed dense infiltrations of large monocytic cells in the muscle layer Hartmann's (261) patient was a 31 year old man who had several recurrences of yellowish "lentil to cherry" sized cutaneous nodules on the upper lip cheek forearms legs chest and groin The hemogram revealed 162 000 white blood cells per cu mm with 82 per cent neutrophils 15 per cent myelocytes and 2 per cent eosinophils Histologic examination revealed infiltration around

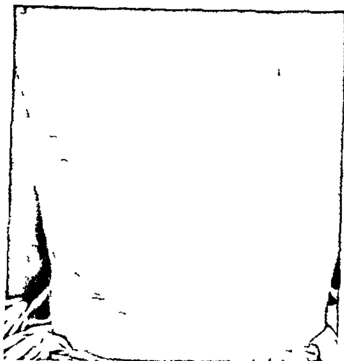


Figure 32 Elevated leukemic nodules on the back (Courtesy of William Ford M D, Univ of Illinois College of Medicine

masses about the sweat glands, adipose tissue, blood vessels and hair follicles The reticulum about these infiltrations was increased and active in the formation of leukemic cells The *predominant cells were blast forms with occasional* neutrophilic myelocytes and there were large, roughly rounded, monocytes having large nuclei with frequent irregular forms Mitotic figures were not common and neutrophilic leukocytes, metamyelocytes and phagocytic cells were occasionally present At autopsy, histologic examination of a small subcutaneous nodule revealed numerous blast cells with frequent early neutrophilic myelocytes *This* suggested a primary autochthonous cutaneous derivation of the leukemic blast cells from the local reticuloendothelial elements rather than infiltrations of leukemic *cells of metastatic origin, according to* Paul and Limarzi The implications are great, they stated that the rapid pouring out of myelocytes into the peripheral blood

per cent myeloblasts and 35 per cent myelocytes Histologic study of a cutaneous nodule showed a perivascular infiltration consisting mainly of myelocytes and myeloblasts Tennenbaum (677) described a 60 year old man who first noted pain in the lower sternum and shortness of breath on exertion one year previously Six weeks before examination painless bluish colored cutaneous "spots" appeared which became nearly generalized within a few weeks Simultaneously the dyspnea increased and insomnia and pain in the left hypochondrium developed The skin was mottled and covered with small petechiae and larger confluent hemorrhagic "spots" which were most pronounced on the trunk and flexor surfaces of the extremities Some of the purpuric lesions were bright red in color while others appeared to be fading The oral mu [illegible] agic [illegible] ele- [illegible] pap ules and nodules involving the trunk and extremities and a few on the face behind the ear and in the oral cavity Only a few lesions on the tonsils and in the oral cavity were ulcerated A few larger tumors 1 5 cm in size and a smaller "hazelnut" sized lesion were present on the left cheek They were dark blue in color glistening globular and sharply circumscribed A similar "dime" sized tumor and one 2 cms in diameter were present on the lower one half of the sternum and a few others were scattered over the body The largest of "quarter" size was markedly elevated above the skin surface of the left thigh There was submaxillary maxillary and inguinal lymphadenopathy The peripheral white blood cells consisted of 29 5 per cent polymorphonuclears 2 per cent myelocytes 1 5 per cent myeloblasts 8 per cent monocytes and 59 per cent lymphocytes

Emile-Weil and Isch Wall (165a) reported a patient with granulocytic leukemia in whom six weeks before death cutaneous tumors developed simultaneously with *the appearance of* "undifferentiated" cells *in the peripheral* blood Sanmicandro (596a) reported a 25 year old man who had granu

the hair follicles and other cutaneous appendages The capillaries were markedly dilated and filled with cells having a positive oxidase reaction The diagnosis of granulocytic leukemia was confirmed at autopsy

Saslawsky and Ioffe (599) reported a 34 year old man who had multiple cutaneous nodules There was diffuse lymph adenopathy and splenomegaly The peripheral white blood cells ranged from 9,000 to 37,000 per cu mm, with varying numbers of immature cells Autopsy revealed hyperplasia of the lymph nodes and spleen and lymphoid infiltration of the cutaneous tissues Despite the histologic diagnosis of "round cell sarcoma," this case was considered to be chronic leukemia which had developed into granulocytic leukemia

Bruusgaard (81) reported a 38 year old man who presented numerous bluish, isolated, confluent cutaneous nodules, of "pea" size or larger, extending into the subcutaneous tissue These lesions involved the trunk and extremities and larger flat infiltrations were present in the lower dorsal and sternal regions The hemogram revealed 410,000 white blood cells per cu mm, with 60 per cent neutrophilic myelocytes, 18 per cent polymorphonuclears, 6 per cent eosinophils, 4 per cent basophils, 8 per cent lymphocytes, and 8 per cent monocytes *Another patient reported by Bruusgaard was a 30 year old* man who had numerous hard, bluish, elastic, purpuric, infiltrated cutaneous lesions involving the thighs and back and nearly generalized lymphadenopathy There were 70,000 peripheral white blood cells per cu mm, with 85 6 per cent myelocytes 6 2 per cent myeloblasts and 1 per cent eosinophils Histologic study of the skin showed profuse perivascular infiltrations with myeloblasts myelocytes, neutrophils and eosinophils

A 17 year old girl reported by Lublner (402), had been ill for seven months She had numerous bluish red or brown, fibrocartilaginous, irregularly distributed cutaneous *nodules* There was lymphadenopathy and hepatosplenomegaly The hemogram varied from 44,000 to 116,000 white blood cells per cu mm, with 17 per cent polymorphonuclears, from 13 to 74

which Freund believed would justify the conclusion that cells of loose connective tissue fat and vessel walls transform into leukemic blood cells Following roentgenotherapy, the histologic picture of the skin showed transitional stages in which the reversion of leukemic cells to connective tissue cells and connective tissue was apparent

A 30 year old "Javanese described by De Langen (145), had intense pruritus for one week preceding the appearance of cutaneous tumors on the head neck and trunk These lesions increased rapidly in size and central necrosis developed in the larger tumors The peripheral white blood cells increased from 113 000 to 300 000 per cu mm within a few weeks time and peroxidase staining produced a positive reaction Histologic examination of a cutaneous lesion revealed numerous monomorphous round cells Many of these cells showed mitosis but the the oxidase reaction was negative Barney's (28b) patient a 55 year old man had been ill for six months He had approximately 10 noninflammatory cutaneous papules involving the lower lip and gums which were of "pinhead" size and were the color of the surrounding mucous membranes There were numerous "pinhead to cherry" size brown to purple firm noninflammatory cutaneous nodules on the trunk and to a lesser extent on the thighs and upper arms The majority of these lesions were elevated and movable with the skin while a few were deeper in the subcutis The lesions were most prominent on the abdomen and lower part of the back The hemogram revealed 24 600 to 83 000 white blood cells per cu mm with 10 to 31 per cent neutrophils 1 to 3 per cent eosinophilic myelocytes and 1 to 7 per cent myeloblasts He died two months after the cutaneous involvement occurred Histologic examination revealed the corium to be infiltrated with granulocytic cells which had a positive oxidase reaction

Rolleston and Fox (572b) described a 58 year old woman who had oval shaped slate grey to plum colored cutaneous nodules on the back and on both thighs with some isolated nodules on the calves and upper arm The lesions were rough

locytic leukemia for two years before a polymorphous cutaneous eruption appeared These lesions were yellowish colored vesicles papules pustules and nodules which were disseminated over the skin of the entire body the most numerous and prominent lesions being "pea to nut sized nodules There was hepatosplenomegaly and the hemogram revealed 560 000 white blood cells per cu mm with 52 per cent myelocytes Histologic study of a cutaneous lesion showed a dense infiltration of myeloblasts myelocytes eosinophils and megakaryocytes in the deep cutis He considered the cutaneous infiltration to be the result of localization and colonization of peripheral blood cells in the skin

The patient reported by A M H Gray (239) was a 36 year old man who first noted a dark" cutaneous nodule on the left cheek six months previously A short time later another nodule appeared on the right cheek and others subsequently involved the forehead extremities trunk and cheeks On examination there were approximately 20 deeply infiltrated "dark plum colored cutaneous nodules the largest being of cherry size He had mild lymphadenopathy Histologic examination of a cutaneous lesion showed diffuse rather patchy infiltration of the dermis and hypoderm which was most marked along the blood vessels and around the hair follicles and sweat glands This infiltration consisted of lymphocytes and plasmacytes The blood picture was that of granulocytic leukemia A 48 year old woman reported by Hudelo *et al* (299) had generalized erythema with slight lichenification of the skin of 28 months duration There were cutaneous papules and small bullae scattered over the body and many nonulcerated nodules on the face She had splenomegaly and the hemogram was typical of granulocytic leukemia Histologic study of a cutaneous nodule disclosed numerous granulocytic cells while the papular and vesicular elements showed only the usual inflammatory features The patient reported by Freund (200 a) presented circumscribed leukemic cutaneous nodules Prior to roentgenotherapy the histologic picture of the skin revealed transitional cell stages



Figure 33 Plum colored true leukemic infiltrated plaques on fore head and nodular lesions on eyebrows and malar prominences (Courtesy of Maurice J Costello M D *A M A Arch Dermat* 71 605 1955)

ed mostly myeloblasts with a few other granulocytic elements Following treatment with procaine penicillin the temperature returned to near normal the spleen and lymph nodes de creased in size and the hemogram showed 2 950 white blood cells per cu mm with 49 per cent polymorphonuclears 50 per cent lymphocytes and 1 per cent myelocytes Histologic study of a cutaneous lesion was reported to show changes compatible with those present in granulocytic leukemia Another patient reported by Costello *et al* (127b case 4) was a 64 year old woman who had marked weakness loss of weight anorexia and severe generalized pruritus for six months She had marked lymphadenopathy in the left axilla and a small hemorrhagic lesion which bled spontaneously on the left leg Several purpuric papules were present on the buccal and vaginal mucosa and a fine vesicular eruption involved the anterior aspects of the chest and abdomen

ly symmetrical in distribution, they were firm, superficial, some slightly tender and involved the cutis rather than the subcutaneous tissue Madden (420b) reported a 50 year old woman who had noted a firm "pimple" just within the "hair line" of the forehead one year previously This lesion increased steadily in size and became a "quarter" sized, slightly raised, dull red plaque The hemogram revealed 35,000 to 52,000 white blood cells per cu mm, with a preponderance of polymorphonuclears, many immature forms of metamyelocytes, myelocytes and progranulocytes Weiss (718) described a patient who had cutaneous lesions of granulocytic leukemia with three large nodules involving the face The lesions had appeared before the peripheral blood changes but within two to three months the blood picture was typical of granulocytic leukemia

Costello *et al* (127b case 2) described a 73 year old man who had weakness, cough and loss of weight for five months and a cutaneous eruption for one year He had been treated for pulmonary tuberculosis three years previously On examination, he had cervical lymphadenopathy, the inguinal and epitrochlear lymph nodes were palpable and there was hepatosplenomegaly There were symmetrical, hyperpigmented, oval, macular, 'large' and "dime" sized irregular infiltrated cutaneous lesions involving the face, trunk and extremities There were plaque like, nonpruritic, purplish-red nodules which showed various degrees of infiltration Some on the face and scalp were rounded and of egg" size, and there were diffuse, flat infiltrations over the eyebrows and malar prominences Roentgenogram of the chest revealed infiltration of lower part of the right lung and of the right apex of the lung, which contained a large cavity The sputum examination disclosed numerous acid fast bacilli and the Rumpel-Leede test was positive The hemogram disclosed 6 5 gm hemoglobin, 2,050,000 red blood cells and 13,600 white blood cells per cu mm, with 21 per cent polymorphonuclears 12 per cent lymphocytes, 66 per cent myeloblasts, 1 per cent myelocytes and an occasional monoblast The sternal bone marrow study show-



Figure 35 Horseshoe shaped purpuric infiltrated true leukemic (granulocytic) lesions surmounted by bullae on inner aspect of left thigh (Courtesy of Maurice J Costello M D *A M A Arch Dermat*, *71* 605, 1955)

form or crescentic in shape Five months later she had fever, arthralgia tender cutaneous nodules and petechiae The first histologic study was reported to show erythema nodosum" and the second was "suggestive of Weber Christian disease" However after reviewing these sections, Sachs (593) concluded that "the diagnosis is most likely myelogenous leukemia" The following month she had infiltrated "erythema bullosum like" lesions on the toes and extremities and hepatosplenomegaly had developed The hemogram revealed 7 gm hemoglobin 2 300 000 red blood cells and 5,200 white blood cells per cu mm with 8 per cent myelocytes The erythrocyte sedimentation rate was 66 mm in one hour Following corticotropin therapy she was afebrile for three days when fever of 104° to 105° F developed and new purpuric, infiltrated lesions appeared on the legs and a large, phlegmonous deep inflammatory, necrotic lesion covered with bullae, ap



Figure 34 Massive granulocytic leukemic infiltrate composed predominantly of polymorphonuclears and larger cells showing a definite cell outline with somewhat foamy cytoplasm and oval vesicular nuclei Low power (Courtesy of Maurice J Costello, M D *A M A Arch Dermat*, *71* 605 1955)

There were numerous 1 to 2 cm, reddish brown, purpuric nodules on the lips and back She had severe pruritus, hepatosplenomegaly and marked pain of the right sciatic nerve During the following two months the hemogram varied from 62 to 40 per cent hemoglobin 2 800,000 to 1,600,000 red blood cells and 44 000 to 100,000 white blood cells per cu mm The autopsy revealed secondary myeloid leukemic infiltration of all the internal organs skin and lymph nodes There were petechiae and ecchymoses of the panniculus, peritoneum, skin conjunctivae kidneys pericardium, pleura lungs and stomach They (127b case 1) also described a 16 year old girl who had erythematous "erythema nodosum like" cutaneous lesions on the lower extremities eight days after an appendectomy She had chills, fever, weakness, leukocytosis and an elevated erythrocyte sedimentation rate These persistent cutaneous lesions were infiltrated, surmounted by bullae and varied in size and shape Many were arci

cells decreased to 8 500 per cu mm with 15 per cent blast cells Subsequently, several clinical remissions followed corti sone therapy ("in fairly high doses) and hematologic re mission followed the administration of 6 mercaptopurine However, 13 months following the onset of illness she had progressive anemia and loss of vision and four days later generalized convulsions coma and clinical evidence of cere bral hemorrhage preceded her death

Case Report A 43 year old man had marked weak ness slight dyspnea and vertigo for two years One year previously "cramps" had occurred in the calves as well as gastrointestinal symptoms and severe neu ritis in the right arm and right upper chest and shoulder which persisted for two weeks and left a residual nod ule near the third right costal cartilage and aching of the right arm These symptoms were accompanied by increased sweating elevation of the temperature in the evening and generalized pruritus Two weeks later neuritis developed in the right leg and left shoulder and a nodule in the left clavicle Numerous nodules then appeared on the back became swollen and ulcer ated and spread to involve the entire back and he had severe pain below the left costal margin On exam ination there were innumerable leukemic nodules and furuncles involving the scalp arms neck trunk and legs The hemogram disclosed mild secondary anemia and 150 000 white blood cells per cu. mm. The mucous membranes of the mouth were dry and bright red in color and there was a thick dry white exudate around the crevices and fissures while the tongue was deeply fissured red and dry The entire cutaneous surface was covered with subcutaneous and cutaneous ulcerating leukemic infiltrations and nodules in the region of the third right costal cartilage and the left clavicle Many superficial lymph nodes were enlarged and nearly the entire abdomen was filled by the enlarged spleen Two months later severe pains suddenly developed in the



Figure 36 Lesions from skin showing infiltrate surrounding blood vessels and sweat glands Process extended into deep portions of corium and into subcutaneous layer Low power hematoxylin stain (Courtesy of Maurice J Costello, M D *A M A Arch Dermat*, *71* 605, 1955)

Figure 37 Granulocytic infiltrates composed predominantly of polymorphonuclears and larger cells in which the nuclei are somewhat oval or round and slightly vesicular High power (Courtesy of Maurice J Costello, M D *A M A Arch Dermat*, *71* 605, 1955)

peared in the left axilla She improved with cortisone therapy and the cutaneous lesions gradually subsided The sternal bone marrow was hyperplastic with an increase in immature granulocytes The peripheral white blood cells showed 12 per cent myelocytes and 2 per cent myeloblasts The diagnosis of granulocytic leukemia was established The following month there were 21 per cent myeloblasts and 9 per cent progranulocytes in the peripheral blood The next month there were 20,000 white blood cells per cu mm, with 71 per cent myeloblasts Following the administration of 6 mercaptopurine and superficial roentgenotherapy, the white blood

firm cutaneous nodules over the left breast The lesions increased progressively in size and number during the following three months until they involved the greater portion of the chest, the axillae and the inner surface of the forearm Some lesions coalesced forming somewhat larger nodules while some faded and became "waxy" in appearance and still others disappeared completely leaving no scarring or pigmentation Two months later, histologic study of a cutaneous nodule disclosed massive myeloblastic and granulocytic infiltration of the cutis and hypoderm These infiltrating cells, which gave rise to the formation of the nodules, consisted of immature cells of the granulocytic series The predominating form were the nongranular myeloblast and monocytic cells having a round to oval nucleus and moderatly abundant cytoplasm There were scattered eosinophilic monocytic myelocytes together with less mature myeloblastic forms, which were not numerous Some eosinophils and polymorphonuclears were present among the infiltrating cells

Two patients who had cutaneous lesions associated with granulocytic leukemia were reported by Thewes (679) The first was a 15 year old girl whose initial manifestation of the disease was the appearance of specific cutaneous nodules on the trunk and extremities The second a 59 year old woman, had nonspecific cutaneous hemorrhage of the face which showed a tendency toward ulceration a few weeks before death Tagami *et al* (673) reported a 64 year old man with subacute granulocytic leukemia who had marked, widespread cutaneous infiltration which produced leonine facies Severe necrotic stomatitis developed two months before his death, which occurred six months after onset of the disease Nusso and Cordero (485) reported a 16 year old boy who had medullary aplasia throughout the course of subacute granulocytic leukemia There were numerous pink nodules and small tumors involving most of the cutaneous surface which showed on histologic study, infiltrations of granulocytic cells in different stages of maturation, both in the dermis and in the hypoderm

Case Report A 60 year old man complained of

right sacroiliac joint and radiated transversely across the sacral spine and down the right thigh This pain had remained intractable for two days However, the cutaneous lesions had almost completely regressed during the previous two months The mucous membranes of the mouth were pale and there were hemorrhagic areas on either side of the septum and on the right inferior turbinate and small hemorrhagic areas on the right tonsillar pillar He died one month later and autopsy disclosed granulocytic leukemia

Netherton's (473 i) patient was a 19 year old boy who had cutaneous lesions on the anterior surface of the trunk and lower extremities These discrete, infiltrated lesions ranged from a few mms to 10 cms in size and were purple, dark red or violaceous in color The majority of the lesions were nodular and involved both the subcutis and dermis The newer lesions were light brown in color and not elevated, while the older lesions were bluish purple and elevated

The patient described by Goldhamer and Barney (231) was a 41 year old man who had many purpuric areas on the right leg There was intense pigmentation on the exposed surfaces of the legs, the conjunctivae were pale and many areas of hemorrhage were present on the buccal mucosae There was hepatosplenomegaly and marked generalized lymphadenopathy On examination, 16 months later, he had three 'half cherry" sized cutaneous nodules on the right side of the chest and the same number on the right tibia These lesions were discrete and attached to the overlying skin but not bound to the underlying structures They were firm, non tender, circumscribed and of a rubbery consistency The skin was dull, erythematous and showed no evidence of hemorrhage Other split pea sized nodules subsequently appeared in the same areas Histologic examination of a cutaneous nodule revealed infiltration of granulocytic cells, in nodular formation, present deep in the corium overlying the adipose tissue

Hollander *et al* (292) reported a 50 year old woman who had 10 bluish, slightly elevated, painless, nonpruriginous,

had appeared there was a 25 cm granulomatous lesion which had a necrotic center on the anteromedial aspect of the right thigh and several smaller ulcerating satellite lesions as well as nodular bluish lesions some ulcerated involving the right leg There were numerous erythematous lesions varying from a few mms to several cms in size on the trunk but most marked on the left breast The larger lesions were ulcerated The hemogram revealed 59 per cent hemoglobin 4 180 000 red blood cells and 15 250 white blood cells per cu mm with 52 per cent polymorphonuclears 19 per cent band forms 2 per cent eosinophils 14 per cent lymphocytes and 13 per cent monocytes Histologic study of the cutaneous lesions revealed granulocytic leukemia cutis Sternal bone marrow examination disclosed a moderately hypercellular marrow The megakaryocytes appeared normal The nucleated red blood cell white blood cell ratio was 1 5 The erythropoiesis was normoblastic The granulopoiesis showed a shift to the left with marked toxicity The plasmacytes and eosinophils were somewhat increased in number An increase of iron pigment was also noted The diagnosis was abnormal marrow nonspecific pattern"

D Chloroma Chloroma is generally considered to be a form of granulocytic leukemia which differs only in that the cutaneous lesions are of a green color Literally chloroma means a "green colored tumor" The disease is characterized by the deposition of tumor like aggregations of granulocytic cells particularly in the subperiosteal regions of the skeleton typically in the orbits and about the cranial bones The fresh preparations of the tumors are of a greenish color which fades on exposure to light The disease may become manifest in various degrees some show only a green coloration of the infiltrated organs while others may present tumors which are typical of leukemic nodules excepting for the green color Because of these variations Brannan (74) concluded that there is no sharp distinction between chloroma or "chlora

dyspnea on exertion and "tiredness" for three months He had been treated with "shots" and transfusions of whole blood for "anemia" He presented cutaneous ecchymoses over both antecubital spaces and purpuric lesions on both lower legs Two months later the purpuric lesions had become generalized, the liver was palpable seven cms below the costal margin, the spleen was palpable, and there was moderate inguinal and epitrochlear lymphadenopathy The skin had an icteric tinge and the conjunctivae and oral mucosa were pale Laboratory studies revealed one plus albumin in the urine and the hemogram showed 25 per cent hemoglobin, 1,910,000 red blood cells and 2,000 white blood cells per cu mm, with 6 per cent polymorphonuclears, 16 per cent band forms, 1 per cent eosinophils, 5 per cent basophils, 25 per cent lymphocytes, 12 per cent myelocytes and 30 per cent metamyelocytes Biochemical examinations revealed the total protein to be 6 gm/100 cc, total cholesterol 75 mg/100 cc, icteric index 18 units, alkaline phosphatase 2 0 units (Bodansky), and thymol turbidity 4 1 units Histologic study of a cutaneous lesion showed the typical findings of granulocytic leukemia

Case Report A 48 year old Negress first noted redness and pruritus of the right thigh four years' previously Despite topical therapy, the pruritus persisted and several months later the area became crusted Two years later, an 8 cm, raised lesion had appeared in the same area which became ulcerated several months later This lesion gradually enlarged to 16 cms and became fungating *The following year red, raised* nodules appeared on the left breast which gradually enlarged and ulcerated in the center Subsequently, similar lesions appeared on the trunk There were also firm, bluish cutaneous nodules on the right leg and knee which had been present for one month On examination four years after the initial cutaneous lesions

V

MONOCYTIC LEUKEMIA

A. History

In 1912 Schilling (605a) was able to demonstrate a third type of white blood cell, with the use of new technics He called this white blood cell the "monocyte" The following year Reschad and Schilling (555) described a patient whom they believed had "monocytic leukemia," as well as cutaneous manifestations consisting of purpura, maculopapular and nodular specific lesions

Although other investigators had previously reported cases which Evans (172a) believed warranted inclusion in this group, Reschad and Schilling were the first to state that a third type of leukemia could occur and reported a case exemplifying this concept

B. Etiology

Monocytic leukemia appears to occur much less frequently than either the lymphocytic or granulocytic type In reviewing 600 consecutive cases of leukemia, N Rosenthal and Harris (578a) found a relative incidence of 66 7 per cent granulocytic, 27 6 per cent lymphocytic and 1 9 per cent monocytic leukemia Among 76 cases studied over a period of *four years*, Doan and Wiseman (149) found 34 per cent granulocytic, 47 per cent lymphocytic and 16 per cent monocytic leukemia Estimates concerning the frequency of monocytic leukemia vary from 18 to 20 per cent (Gordon 237) to 2 per cent (N. Rosenthal and Harris 578a), of all patients having leukemia

leukemia" and granulocytic leukemia

According to Kandel (325) the green pigment is apparently a lipochrome and is believed to contain iron Although the color disappears about one hour after exposure to air, it may be restored with the application of hydrogen peroxide

Chloroma occurs more frequently in men than in women and usually affects young persons The youngest patients, both infants, were described by Stransky (659b) and Morrison *et al* (462) A three month old infant who had granulocytic leukemia with chloromatous tumors was reported by F S Jones *et al* (320) Cutaneous nodules occurring in infants were also described by Cross (131) and H M Keith (335b) A seven year old Negro boy who had cutaneous nodules was presented by Goodman and Iverson (236) A 34 year old patient, reported by Caird (91), had about 20 raised, purplish cutaneous nodules, from 1 25 to 6 25 cms in size, on the trunk Similar nodules were present on both cheeks and on the eyelid The cutaneous lesions were the only manifestation of chloroma

The specific cutaneous manifestations associated with chloroma are regarded to be in the same group of tumors as those comprising cutaneous granulocytic leukemia Other cases having green cutaneous nodules were described by Bramwell (72) in a 25 year old man, by Hitschmann (287a) in a 26 year old man, and by Jacobeaus (312) in a 35 year old man

Type of Eruption	*Men*	*Per Cent*	*Women*	*Per Cent*
Purpuric	22	69	10	31
Maculopapular	10	67	5	33
Nodular	7	64	4	36
Suppurative	9	90	1	10
Exfoliative	5	84	1	16
All Cases	–	71	–	39

tion of a slight increase of suppurative and exfoliative cutaneous eruptions in men, there were no significant differences for the various eruptions

The occurrence of monocytic leukemia in children was reviewed by Court and Edward (128) They found the youngest child was 11 months of age, while the average age was six years and three months Only 40 per cent of the monocytic group were under five years of age, as compared with 64 per cent of the lymphocytic group, in which the average age was four years and three months Their studies suggested that monocytic leukemia tends to occur somewhat later in childhood than the other types of leukemia This is in contrast to the general opinion that leukemia in children tends to occur during the first four years of life, as mentioned by Whitby and Britton (725a) In Court and Edward's series, boys were more frequently affected than girls, the ratio being 3 2 This is similar to the ratio found in adults They found that oral lesions occurred in 52 per cent of the cases of monocytic leukemia and in 20 per cent of the lymphocytic leukemia cases The mouth lesions consisted of soreness bleeding from the gingivae and swelling and necrosis of the mucous membranes, which sometimes extended to the tonsil or to the soft palate

Although oral lesions may cause some of the most striking symptoms in adults, in whom necrosis of the mucous membranes may reach the degree of diffuse cellulitis they concluded that only the milder forms of oral involvement occur in children and it was a prominent symptom in only two of their cases According to Court and Edward, the belief held by Forkner (192a) that diffuse and marked swelling of the mucous membranes, particularly of the gingivae, with ulcera-

Although Isaacs and Sturgis (308b) pointed out the fallacies involved in attempting to arrive at a general percentage, they believed there would probably be an increase in the number of reports of this disease when knowledge regarding it became more general Because the diagnosis is made primarily on study of the circulating blood cells, Evans (172a) believed that higher percentages of cases of monocytic leukemia would be reported by laboratories in which the supravital staining technic is a routine procedure

1 *Age·* *Age does not seem to be an important* factor in monocytic leukemia Gittins and Hawksley (226) reported an infant of less than one year and MacKeith and Bailey (417) described a patient 81 years of age

Fairburn and Burgen (175) listed the relationship of age to the type of cutaneous lesion present in monocytic leukemia

	Age Years					
Type of Eruption	*Birth 19*	*Per Cent*	*20-39*	*Per Cent*	*More than 40*	*Per Cent*
Purpuric	6	19	10	31	16	50
Maculopapular	2	12	5	32	9	56
Nodular	1	9	4	36	6	55
Suppurative	0	—	1	10	9	90
Exfoliative	0	—	2	33	4	67
All Cases	7	14	16	32	27	54

According to these figures, more than 50 per cent of all patients having monocytic leukemia were more than 40 years of age, in contrast to the age incidence in acute lymphocytic leukemia and granulocytic leukemia in which the average age of incidence is less than 40 years When the age incidence in relation to the type of cutaneous lesion present is considered, there are no significant differences

2 *Sex* Approximately twice as many cases of monocytic leukemia have been reported in men (Adler 3) as in women (*Flaherty et al* 187) (table, p 109)

Among these cases, 71 per cent were men, which is similar to the sex distribution for all cases of monocytic leukemia as mentioned by Whitby and Britton (725a) With the excep

metabolism (tuberculosis, Niemann-Pick disease, Schuller-Christian disease, Gaucher's disease and, possibly, Hodgkin's disease) and, (4) the fatty vacuolization of the monocyte It was their opinion that monocytic leukemia begins as a disturbance of fat metabolism which results in monocytic proliferation They believed that chronic forms of the disease could possibly be controlled to some extent by "care of this disordered state"

The various concepts concerning the origin of the different cell types were listed by Evans (172a)

1 The unitarian view, which assumes that all blood cells rise from one blast cell, the lymphoblast Few hematologists still adhere to this concept

2 The dualistic view, in which all cells of the peripheral blood are believed to originate from the lymphoblast and the myeloblast

3 The trinitarian view, which holds that all blood cells stem from the myeloblast, the lymphoblast, and the rubriblast

4 The modified dualistic view with separate macrophage origin, in which three blast cells are postulated for three white cells (myeloblasts, lymphoblasts, and monoblasts) and one for the red blood cells (rubriblast), together with a separate origin for the clasmatocytes

At present, the majority of investigators favor the reticuloendothelial origin of the monocyte However, many others believe that the site of origin of the monocyte should not be limited specifically to the reticuloendothelial system but should be included in the broader

tiation and proliferation

the numerous conflicting

monocytic cells

The morphologic features which are characteristic of the monoblast were described by Osgood (496a) as the large size of the cell (from 15 to 30 microns in diameter), the fine chromatin structure of its nucleus, which is similar to that of the myeloblast but perhaps even more transparent, and its uniform nucleoli, which is usually round or oval The cyto-

tion and necrosis is characteristic of monocytic leukemia and not usually present in other forms of acute leukemia is not substantiated *in monocytic leukemia in children* They found cutaneous lesions to be present in 18 per cent of the patients with monocytic leukemia and in none of those who had lymphocytic leukemia These lesions consisted of (1) firm painless cutaneous nodules which on histologic examination showed a preponderance of monocytic cells or their precursors and (2) widespread staphylococcic infection such as furuncles or carbuncles

An 11 year old boy who had a cutaneous eruption of scanty large vesicular efflorescences was reported by Plum and Thomsen (529b) The spleen and liver were palpable but there was no cervical lymphadenopathy The bullous eruption progressed rapidly until almost the entire cutaneous surface was involved The new vesicles were hemorrhagic and the slightest trauma caused loosening of the epidermis He died 10 days after onset of the disease The histologic studies at autopsy revealed monocytic leukemia pneumonia and large agglomerations of monocytic cells in the skin and bone marrow

C Pathogenesis

That monocytic leukemia is not a disease but merely a symptom complex and that this syndrome is an unusual reaction to infection was considered by Krahn (353) Sternberg (652) and others Evans (172a) believed there were several instances in which there was a monocytic response to microorganisms

That a disturbance in lipid metabolism may play a part in monocytic leukemia particularly in the chronic form was suggested by Dorn and Wiseman (149) who presented supporting evidence for this theory They listed these probabilities as (1) the selective phagocytosis of fats by monocytes (2) the evidence of excess of plasma lipids in monocytic leukemia (3) the occurrence of monocytic hyperplasia in other diseases associated with proved disturbance of fat

(310), "aleukemic reticulosis" by Dameshek (139b), "leukemic reticulo endotheliosis" by Downey (152a, b) and Ewald (173) and as "malignant reticulosis" by Cazal (108).

D. Symptoms

1. General. The symptoms and signs of monocytic leukemia were listed by Isaacs and Sturgis (308b) in order of their frequency

Symptom	*Per Cent of Cases*
Weakness	100
Clinical splenomegaly	82
Fever	82
Loss of weight	77
Mouth lesions (cheeks, gums, pharynx)	73
Pain	64
Hepatomegaly	59
Albuminuria	50
Purpura	41
Cervical lymphadenopathy (usually mild)	41
Cutaneous lesions (other than purpura)	36
Epistaxis	36

Although some early investigators assumed that monocytic leukemia occurred only as an acute disease, there is now little doubt that, clinically, there are acute and chronic forms as well according to Evans (172a) The majority of cases have been of short duration after the diagnosis was established As in other forms of leukemia, the disease is usually "leukemic" However the "aleukemic" or "aleukemic interval" type may occur in monocytic leukemia In a typical case of acute monocytic leukemia, Evans stated, there is a short prodromal period of weakness and malaise which is usually followed by the abrupt onset of gingivitis, painful teeth, bleeding gums, sore throat ulcer of the tongue or any combination of these symptoms There may be gastrointestinal symptoms and, occasionally a history of dysuria or hematuria Invariably the patient is extremely ill, prostrated and pallid, with a high fever and tachycardia, while hemorrhagic areas frequently

plasm ranges from basophilic to deeply basophilic and is greater in proportion to the size of the nucleus than that of the myeloblast or lymphoblast Monoblasts are difficult sometimes impossible to distinguish from myeloblasts or lymphoblasts The chief difference lies in the more frequent occurrence of fine diffuse azurophil granules in the cytoplasm *of the monoblast similar to those of the mature monocyte* This differentiation cannot be made with peroxidase staining since all these cells give a negative peroxidase reaction

The accepted view at the present time is that expressed by Cunningham *et al* (134) who recognized three types of leukocytes each arising from a common mesenchymal rest and stem cell The granulocytic series arises from the myeloid tissue in the bone marrow and the lymphocyte from the lymphatic tissue in the lymph nodes spleen and diffuse lymphoid tissue of the body The monocyte arises in the connective tissue from the so called histiocyte or the reticulo endothelial system The three respective types of leukemia may occur if this theory is correct

Monocytic leukemia is divided into the Schilling and Naegeli types The Naegeli type is considered to be a variant *of granulocytic leukemia Although this classification* of monocytic leukemia is still accepted by some investigators others believe that the rapid advances in hematologic research appear to indicate this view is no longer tenable

In a study of histiocytic and monocytic leukemia Belding *et al* (41) emphasized the differences between the two types of so called monocytic leukemia Although Downey (152b) and others have recognized two distinct types the Naegeli and Schilling they nevertheless include both under the term monocytic leukemia However Belding *et al* considered the Naegeli type to be monocytic leukemia and the Schilling type to be histiocytic leukemia The differences between these two types of leukemia has also been mentioned by Montgomery and Watkins (459c) and Watkins and Hall (710b) Histiocytic leukemia has been variously designated as histioleukemia by Leitner (379) reticulosis" by Israels

(310), "aleukemic reticulosis" by Dameshek (139b), "leukemic reticulo endotheliosis" by Downey (152a, b) and Ewald (173) and as "malignant reticulosis" by Cazal (108)

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Figure 38 Ulcer of the tongue in a child with monocytic leukemia

appear in the skin In the acute form of the disease, involvement of the gums may consist of proliferation, ulcerated lesions, or angina with a 'dirty grey" membrane However, in the chronic form, or during periods of remission, these symptoms are not pronounced, although there are often complaints of weakness, loss of energy and malaise, and cutaneous lesions of long duration, such as nodules, ulcers and exfoliative dermatitis, are frequent Lymphadenopathy and hepatomegaly may, or may not, be present

The following features were listed by Forkner (192a) as being typical of monocytic leukemia (1) Extremely marked gingivitis and stomatitis (involvement of the mucous membranes is limited to small hemorrhages and ulcerations in acute granulocytic and lymphocytic leukemia), (2) cutaneous changes, (3) no generalized lymphadenopathy (as in acute lymphocytic leukemia) (4) absence of, or only slight, splenomegaly, and (5) a greater tendency toward an acute course The subacute and chronic forms tend to have unusually complete clinical and histologic remissions according to Forkner

Figure 39 Hemorrhagic lesions associated with monocytic leukemia

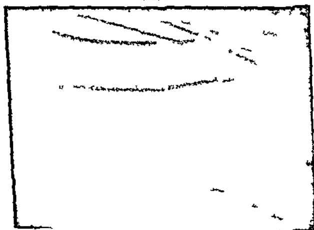


Figure 40 Hemorrhagic lesions associated with monocytic leukemia



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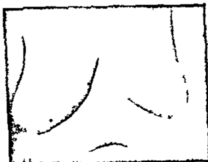


Figure 42 Deep seated shotty papular lesions (*A M A Arch Dermat* 73 189 1956)

which may lie deeper in the corium and are frequently more easily detected by palpation than visibly Both of these types of eruption may involute or disappear completely "Minute red dots and fine bluish red lines" may appear in the maculopapular type and the lesions may become slate blue in color and slightly indurated Frequently "faint grey spots which give the skin a mottled appearance" result from involution of the lesions The deeper papules are frequently "shotlike" and "may show fine reddish lines although induration and the development of "walnut" sized nodules (Bykowa 90) may occur There may be erythematous acutely inflamed large furuncle like indurations which become soft and slough in the center Usually multiple petechiae like lesions involve both the skin and mucous membranes before death However mucous membrane hemorrhages are not as frequent in monocytic leukemia as in other forms of leukemia

H E Freeman and Koletsky (199) found the early infiltrated cutaneous lesions of monocytic leukemia may resemble those of mycosis fungoides and the coalescent nodules may form plaques which resemble Boeck s sarcoid They reported that specific cutaneous lesions occurred in 10 per cent of the monocytic in 8 per cent of the lymphocytic and in 1 per cent of the cases of granulocytic leukemia They described the lesions as being of a pale color shotty and papular situated deep in the corium and more apparent on palpation than visually

2. ***Cutaneous Manifestations.*** The cutaneous manifestations of monocytic leukemia usually consist of nonspecific lesions such as ulcerative gingivitis, petechiae and subcutaneous hemorrhages, according to Mercer (443) He described the two types of specific c taneous lesions which are commonly present as (1) Red or brown macules and papules which usually later become blue in color, and (2) pale, shotty papules which lie deeper in the skin and may develop into larg er nodules The nodules may either disappear or break down to form ulcers, while bullae sometimes occur One or more cutaneous lesions are usually present during some stage of monocytic leukemia, according to Mercer, and occur more frequently in monocytic leukemia than in other types of leukemia He also noted that the cutaneous lesions resemble those present in secondary syphilis In reviewing the literature on monocytic leukemia, Mercer fo ind that violaceous nodules were frequently described as an outstanding clinical feature These nodules were sometimes tender and the eruption was usually asymptomatic He concluded that the cutaneous lesions are usually (1) Macules and papules, which initially simulate the cutaneous eruption of secondary syphilis but later become slate-blue in color, and (2) pale shotty papules,



Figure 41 Papular lesions of monocytic leukemia

become darker and deeper violaceous as the lesions became older The lesions which had apparently undergone involution were brown in color and covered with fine sparse scales Furunculosis was the initial symptom in three cases Large indurated ulcers in which histologic examination of the ulcer margin revealed an acute inflammatory reaction and a monocytic infiltration identical to that present in the nonulcerated lesions also occurred in these patients The individual ulcers which were formed by necrosis of large nodules resulted in large deep crateriform ulcers having infiltrated undermined margins Purpura which occurred in 25 per cent of these cases sometimes appeared in patients who had specific cutaneous lesions Two patients in this series had jaundice Hubler and Netherton found that the specific cutaneous eruption was usually of a polymorphous type consisting of light red or brownish colored macules and red to violaceous colored nodules

Doan and Wiseman (149) found that 50 per cent of the patients having monocytic leukemia have cutaneous involvement Osgood (496a) reported that 10 per cent of these patients have specific cutaneous lesions One of his patients presented furunculosis as the initial symptom of the disease

Evans (172a) believed that purpura is a very common finding in monocytic leukemia and although splenomegaly and hepatomegaly are seldom apparent during life there is fre

viewed by Fairburn and Burgen (175) in 1947

a Macules and Papules These cutaneous lesions which are usually generalized have an asymmetrical distribution The typical roseolar maculopapular eruption resembling early secondary syphilis changes from day to day and may be of a cyclic nature There are often minute red dots and fine



Figure 43 Nodular lesions resembling Boeck's sarcoid (*A M A Arch Dermat* 73 189 1956)

Montgomery and Watkins (259c e) also found specific cutaneous lesions present in 10 per cent of the cases They found that the early infiltrated cutaneous lesions may resemble those of secondary syphilis and the coalescent nodules may form plaques which resemble Boeck's sarcoid They found *furunculosis to be a late manifestation of the disease in their* patients

Among 54 patients with monocytic leukemia reported by Hubler and Netherton (298) 24 (48 per cent) had cutaneous manifestations They found that 25 per cent had involvement *of the mucous membranes which consisted of hemorrhage* ulceration or hypertrophy Mucous membrane and cutaneous hemorrhages tended to occur in patients who had a low blood platelet count although several who had normal platelet counts had purpura Three patients had large necrotic ulcers and gangrenous sloughs in the mouth while others had large fungating tumors of the soft palate Among these patients 16 per cent had definitely infiltrated cutaneous lesions from 0 1 to 0 2 cms in diameter which showed little tendency toward scaling Frequently a patient presented macules papules and nodules varying from light pink to violaceous in color which tended to

lar lesions situated in the cutis were present on the lower abdomen and on the loins Some of these lesions were slightly bluish in color The clinical diagnoses varied from secondary syphilis with the primary lesion on the tongue to a drug eruption toxic dermatitis and monocytic leukemia cutis There was a brief clinical improvement following transfusions of whole blood and irradiation of the cervical lymph nodes resulted in disappearance of the cutaneous lesions which left faint mottling and induration However the erythematous macules soon became indurated and slate blue in color Indurated inflamed necrotic nodules appeared on the nose and culture of this lesion disclosed staphylococcus aureus There was visible involution and evolution of the cutaneous lesions during the entire acute course of the disease Shortly before death seven weeks after admission to the hospital numerous small hemorrhagic pinhead" sized lesions appeared on the mucous membranes and new crops of bluish macules developed on other cutaneous surfaces In reviewing the literature Mercer found there is agreement regarding the clinical appearance of the cutaneous lesions and in all the cases he reviewed there had been a diagnosis of monocytic leukemia although some were in the "subleukemic stage He also found there is agreement the leukemic process results from an accumulation of large monocytic cells *in the corium* around the blood vessels and sweat and sebaceous glands

In 1914 Werther (722a) described a patient with "chronic lymphatic leukemia" who had generalized *miliary* cutaneous *infiltrations* The small flat cutaneous nodules showed infiltration about the blood vessels on histologic examination The hemogram revealed 35 000 white blood cells per cu mm and an increase in monocytic cells *He stated* "With such atypical skin lesions we see atypical blood pictures which are difficult to judge because it is the mononuclear cells which are increased"

A 33 year old man reported by Reschad and Schilling (555) *had* gingivitis weakness epistaxis and fever *as* well as widely distributed cutaneous lesions which *resembled* the



Figure 44 Macular and papular lesions on hands and forearms

often leaves faint grey areas which result in a mottled appearance The lesions are sometimes tender to pressure but pain and pruritus are rarely present, Mercer stated, and the cutaneous eruption does not usually precede other symptoms of leukemia He described patients who had cutaneous involvement One (433 case 2) was a 47 year old woman who presented a slightly elevated, tender, indurated, 1 cm lesion on the lower lip There was a 7 mm shallow ulcer, which was moderately indurated, involving the tip of the tongue There was slight firm and tender cervical, inguinal and submaxillary lymphadenopathy The skin and mucous membranes showed slight pallor There was a roseolar, nonpruritic maculopapular eruption on the trunk which was most marked over the lower abdomen and pendulous portions of the breasts Minute red points and very fine, faintly bluish lines, were present in the macules There were similar lesions, some slightly infiltrated, on the inner aspects of both thighs A few small, hard, nodu-

a papule, there was a cellular infiltrate in the corium composed of large monocytic cells having large vesicular nuclei, prominent nucleoli and a vacuolated cytoplasm as well as cells having indented or grooved nuclei, which were considered to be monocytes They described another patient (298 case 6), a 36 year old man, who had brownish red macules and papules and bluish to violaceous nodules on the trunk and extremities They were most marked on the trunk and arms The larger lesions appeared to involve the upper portion of the subcutaneous tissue and there were healing purpuric macules on the trunk and buttocks Histologic studies of an enlarged lymph node showed most of the normal structure to be replaced by a cellular infiltrate With reticulum stain, there was a slight increase of reticulum in the involved areas

A 31 year old woman who presented discrete, firm, "pea to walnut" sized cutaneous papules and nodules, was reported by Loveman (398) This eruption primarily involved the abdomen chest and thighs and resembled a secondary syphilide Some of the lesions appeared to be fixed to the overlying skin The earlier smaller lesions were of normal skin color, while the older lesions were of a purplish hue and, at first glance, many resembled melanomas A gangrenous stomatitis which required surgical intervention, subsequently occurred and the prominence of the nodules varied from day to day Although some cutaneous nodules practically disappeared, new ones continued to appear Bleeding from the mouth and rectum occurred but purpuric and petechial lesions were not noted She died 29 days after admission to the hospital despite repeated transfusions of whole blood and supportive therapy Loveman gave a detailed histologic report of the cutaneous sections This study revealed a thinly cornified atrophic epidermis with short pointed rete pegs There was marked infiltration of the corium by atypical spherical cells which averaged 25 microns in diameter There was a variable amount

lesions of early syphilis, at the onset of the disease However, these lesions enlarged to become nodules and, subsequently generalized petechiae occurred Histologic examination of the cutaneous nodules disclosed innumerable monocytic cells similar to those present in the peripheral blood There were 56,000 white blood cells per cu mm, with 74 per cent monocytes At autopsy, histologic examination of the numerous cutaneous infiltrations disclosed large cells which resembled monocytes, situated primarily around the blood vessels

The patient described by Bingel (47) was a 48 year old man who presented closely distributed, 2 to 4 mm, cutaneous lesions of a bluish color on the abdomen and legs These slightly raised, firm lesions did not disappear on pressure and many appeared to be hemorrhagic There were 15,000 white blood cells per cu mm, with 71 per cent monocytes Histologic examination of the cutaneous lesions revealed accumulations of round cells which were looser in structure than lymphocytes and were usually transversed by one or several blood vessels *A patient who first had a cutaneous eruption resem*bling maculopapular syphilis, which subsequently became purpuric, was reported by Hitschmann and Lehndorff (287b) There were 32,800 white blood cells per cu mm with 76 per cent 'large' monocytes and 10 per cent small' monocytes

Acute monocytic leukemia occurred in the 47 year old woman reported by Sydenstricker and Phinizy (669) She had purplish macules involving the trunk and extremities which became markedly infiltrated before her death There were 71,200 white blood cells per cu mm, with 81 per cent monocytes Histologic studies revealed massive infiltration of monocytic cells which were accumulated particularly around the sweat and sebaceous glands and in the perivascular tissue of the corium Hubler and Netherton (298 case 4) described a 46 year old man who had hypertrophy of the gums and petechiae on the hard palate There were ecchymoses on the thighs and extensive purpura involved the legs, thighs and abdomen Subsequently, infiltrated, firm, pink papules and small plaques appeared on the chest On histologic study of

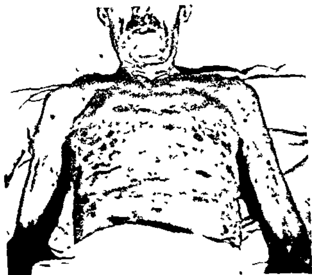


Figure 45 Generalized nodular eruption (*A M A Arch Dermat*, 73 189, 1956)

tioned by Freeman and Koletsky (199) as (1) A more or less generalized dissemination of cutaneous and subcutaneous nodules which may coalesce and form large plaques (this form of the disease may clinically resemble Boeck's sarcoid or mycosis fungoides), (2) the maculopapular type of eruption may simulate secondary syphilis or erythema multiforme, (3) deeper lesions which involve the corium and subcutaneous tissues are nodular or tumorous and must be differentiated from Kaposi's sarcoma, (4) daily changes may be detected in the individual cutaneous lesions which pass through a cycle of development and involution During evolution, their size increases and the color changes from red to bluish red The color becomes dusky red and fades during the period of involution and they finally disappear or leave grey or pale yellowish red macular areas, (5) the lesions sometimes undergo central softening and necrosis before sloughing occurs which results in a crater-like ulceration Bullous or purulent lesions

and slightly granular and a large, eccentric, oval shaped nucleus which was frequently indented or kidney shaped The average size of the nuclei was 18 microns, in long diameter, with a distinctly granular chromatin content, the coarse granules and threads being separated by lighter staining portions A few had nuclei, although they were not a prominent feature The nuclear membrane was sharply defined and occasional mitoses were observed There were some nucleated red blood cells which gave a negative peroxidase reaction In the deeper portions of the corium the infiltrate was diffuse and extensive and, in some areas, the cellular infiltration between the coarse collagenous fibers appeared linear, resulting in a cylindromatous appearance, which was markedly concentrated about small nerves and sweat glands in the deeper portions of the corium There were very few cells present in the subpapillary layer Because of the eccentric position, the indented shape, and the granular character of the nuclei and the large irregular cell bodies, these cells were identified as monocytes and monoblasts and the diffuse infiltration and absence of inflammation indicated that the condition was a neoplasm Although the blood vessels were empty, a recent blood clot contained numerous white blood cells which were similar to those which infiltrated the corium and also a very few normal lymphocytes The histologic diagnosis was cutaneous monocytic infiltration (monocytic leukemia)

b Nodules and Plaques These "shot-like," pale colored cutaneous lesions are usually more readily palpable than visible, and are situated deeper in the cutis than the macules or papules During this stage the lesions may be difficult to differentiate from mycosis fungoides (Montgomery and Watkins, 459c), or from cutaneous sarcoidosis Occasionally, the center of the lesion softens and sloughs, leaving an irregular crateriform ulcer having an indurated base and raised, infiltrated edges Usually some degree of secondary infiltration occurs All stages of transition between macules and papules and nodules and plaques may occur

The following characteristics of these lesions were men-

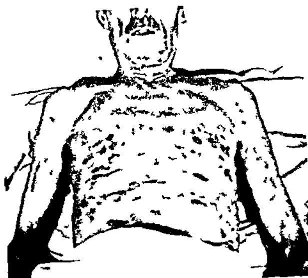


Figure 45 Generalized nodular eruption (*A M A Arch Dermat* 73 189 1956)

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res uts in a crater like ulceration Bullous or purulent lesions

due to superimposed infection may occasionally occur, (6) localized groups of nodules may occur, although generalized dissemination is more frequent The lesions are usually symmetrical, involving all parts of the body (however, one of their patients (199 case 1) presented symmetrical cutaneous lesions involving the upper and lower extremities, abdomen and lower lumbar region), (7) cutaneous lesions may be the first objective symptom and may precede or follow the characteristic hematologic changes The cutaneous manifestations are not pathognomonic of monocytic leukemia and this diagnosis must be established by the hemogram and histologic study of the lesions, and (8) an occasional striking regression following roentgenotherapy is only temporary

Freeman and Koletsky (199) described a 78 year old woman who had multiple cutaneous tumors A firm, purplish red macule had appeared on her left thigh 10 months' previously and subsequently became nodular, increased to 3 cms in size and finally regressed Numerous similar lesions then appeared "every few weeks" on the abdomen, arms and legs These lesions followed the same evolution as the original lesion The nodules were at first of a bright red color but became darker as their size increased and the color gradually faded as they became smaller After several "weeks to months," these lesions disappeared leaving flat, yellowish-red areas However, new lesions appeared simultaneously in previously unaffected areas These symmetrically distributed lesions involved all extremities the thorax, abdomen and lower lumbar region, and a small yellow nodule was present on the right side of the neck These 0 5 to 3 cm lesions were firm, raised and discrete, with occasional 6 cm confluent areas surrounded by a small hemorrhagic area There were accumulations of yellow lipid in some nodules, particularly those on the posterior portions of the legs The deeper lesions were palpable in the subcutaneous tissue and there was no change in the color of the overlying skin There were several small purpuric macules involving the inferior surfaces of the legs A soft, painless, purple colored nodule, "several mms " in diameter,

was present in the right buccal mucosa near the angle of the mouth The cutaneous tumors continued to increase in size and number and she lost a considerable amount of weight Some of the tumors were bullous some fungating and the majority were vascular and bled readily on the slightest trauma An extensive brawny indurated area developed on the inner aspect of the right thigh and was moderately elevated with numerous superficial ulcers A 5 cm subcutaneous lesion on the extensor surface of the left elbow was studied histologically and found to be "monocytic leukosarcoma" During the weeks preceding death the peripheral white blood cells increased from 5 900 per cu mm with 34 per cent monocytes to 126 000 per cu mm with from 56 to 73 per cent monoblasts and a few nucleated red blood cells Coincident with the blood changes many cutaneous tumors increased in size The pathologic diagnoses at autopsy were Monocytic leukemia involving the skin liver spleen adrenal glands kidneys lymph nodes bone marrow and capsule of the pituitary gland as well as arteriolar nephrosclerosis

The patient reported by Sannicandro (596b) was a 37 year old man who had splenomegaly and peripheral lymphadenopathy as well as macular and nodular cutaneous lesions which were associated with hemorrhagic lesions The hemogram revealed from 60 000 to 70 000 white blood cells per cu mm with 48 to 66 per cent monocytes Histologic studies of the cutaneous lesions and an enlarged inguinal lymph node disclosed a diffuse infiltration of monocytic cells The patient presented by Cornbleet and Ebert (123b) was a 50 year old woman who had an infected tooth removed three weeks before generalized lymphadenopathy and deep seated skin colored to slightly brownish generalized cutaneous nodules and papules developed These nonpruritic discrete lesions did not become ulcerated She died three weeks after the apparent onset of the disease A patient reported by Bykowa (90 case 1) had generalized cutaneous lesions consisting of firm brown "lentil" sized nodules some of which became confluent and grew to "walnut" size There were from 5 000 to 10 000 peri

pheral white blood cells per cu mm, with 75 per cent mono cytes A 63 year old man who had "several hundred cutaneous nodules on the legs, arms and trunk was described by L A Mitchell (456). The hemogram was normal, but histologic study of a nodule revealed the corium to be infiltrated by monoblasts which had large vesicular nuclei and a moderate amount of cytoplasm Nucleoli were frequently observed Following arsenic and radium therapy, the majority of the lesions disappeared but later recurred Five months later he became acutely ill, splenomegaly had developed and the peripheral white blood cells numbered 130,000 per cu mm, the majority of which were monoblasts At autopsy there was marked infiltration of monocytic cells in all the organs A patient who had monocytic leukemia cutis consisting of nodular lesions of the skin and gums was reported by Walker *et al* (704)

A 39 year old man, reported by Mercer (443 case 1), had swollen, ulcerated gums and a 2 5 cm ulcer on the hard palate There was moderate generalized lymphadenopathy and the spleen was barely palpable There were numerous bluish, raised, 2 to 5 mm sized, papulonodular lesions scattered over the entire body, including the scalp and forehead, which were most marked on the abdomen and extremities A few other cutaneous nodules, from 1 to 2 cms in diameter, were also present These various sized lesions were of a shotty consistency *and a few of the larger lesions were inflamed*, while others had become necrotic, leaving a punched out center with brownish-yellow crusts Some of the smaller lesions were translucent grey and others retained their normal skin color

One patient described by Hubler and Netherton (298 case 2) was a 33 year old woman who presented numerous dull red to slightly violaceous nodules which had a smooth, unbroken surface, involving the trunk and extremities There was a punched-out ulcer in the region of the anterior pillar of the right tonsil and a palm sized infiltrated plaque just below the right clavicle Another patient (298 case 8) was a 55 year old man who had numerous small, infiltrated, smooth,

round, flesh colored to light red, papules and nodules scattered over the face, trunk, extremities and scalp The pharynx was abnormally red Histologic studies of a cutaneous nodule revealed obliteration of the interpapillary layer of the epidermis which was thinned by an extensive, loosely packed cellular infiltrate that extended throughout the corium and into the subcutaneous tissue This infiltrate consisted almost entirely of monocytic cells with little stroma The cytoplasm was vacuolated and the nuclei were vesicular, round, oval, indented and of a large size There was a fine nuclear membrane and a delicate chromatin network There were one or more nucleoli and some of the nuclei showed transverse folds Few mitotic figures were present Around the pilosebaceous follicles, the infiltrate was abundant and perivascular

Fairburn and Burgen (175) reported a 20 year old man who first had furunculosis, mainly involving the neck and shoulders New crops of these lesions appeared on the shoulder, neck and face six months later followed, in three months, by cutaneous nodules on the right arm which developed to a brawny thickening and later formed shallow ulcers The diagnosis of monocytic leukemia cutis became apparent one year after the first attack of furunculosis At this time the ulcers on the arm had become large and irregular, but they had remained shallow Nearly confluent petechiae, which showed evidence of fading, involved both tibia and a number of brawny, dusky reddish brown, 1 to 15 cm nodules, which had a "metallic sheen," were present on the right arm The larger lesions were superficially ulcerated and the edge of the ulcer was raised everted in outline and of a paler color than other portions of the nodule The floor of the ulcer showed sloughing and was covered by a tenacious, purulent exudate The ulcers were extremely painful and tender to palpation The hemogram revealed 43 per cent hemoglobin, 2,240 000 red blood cells and 277,000 white blood cells per cu mm, with 5 per cent polymorphonuclears, 1 per cent lymphocytes, 90 per cent monocytes, 2 per cent metamyelocytes, 2 per cent myelocytes, and there were 24 000 blood platelets

per cu mm Histologic examination of a nodular cutaneous lesion showed the entire dermis and superficial subcutaneous tissues to be markedly infiltrated by monocytic cells with patchy hyaline eosinophilic necrosis and ulceration The blood vessels were packed with monocytic cells Histologic study of a regressing furuncle showed dense invasion by monocytic cells, while only the hair follicles and sweat glands were invaded by these cells in the less markedly involved edge of the lesion Bone marrow studies revealed the sternal and femoral marrow to be extensively replaced by comparatively large and round, oval, or pyriform shaped monocytes The cytoplasm was ill defined, the nucleus oval, reniform or lobular and finely granular, with occasional hyperchromatic bars There was a distinct nuclear membrane and a moderate number of mitoses were present, but there were no nucleoli The normal architecture of the spleen and lymph nodes was obliterated and they were diffusely infiltrated by monocytic cells, while the liver showed uniform necrosis of the central zones of the lobule, with a heavy peripheral infiltration The nodules which were present in the intestine were uniformly filled with monocytes The histologic picture, in all sections, was described as showing an infiltration by cells of the monocytic series, with primitive and mature types in varying proportions In paraffin sections stained with hematoxylin and eosin these cells were at times indistinguishable from other cells of the lympho reticular series They were usually spheroidal, pyriform or polygonal in shape and had an indistinct outline and lightly eosinophilic cytoplasm The nucleus was usually eccentric and relatively large, showing various shapes from spheroidal to oval to reniform and finally band like, often with a notched or lobulated appearance The chromatin was granular, and frequently a hyperchromatic longitudinal groove, an effect of the nuclear folding was present Nucleoli and mitoses were not prominent In the earlier lesions the infiltration was present between the connective tissue fibers and in the adventitia of the small vessels, but later the sebaceous and sweat glands and the hair follicles became involved There

was a dense invasion of the entire dermis and adjacent subcutaneous tissue Zones of hyaline necrosis and hemorrhage may occur, while the epidermis undergoes degenerative changes which may precede ulceration, and the vessels are filled with monocytic cells When there is suppuration, there is a central area of necrosis which is surrounded by a dense zone of monocytic infiltration There is a light infiltration, mainly confined to the perifollicular areas, present at the periphery. Staphylococcus aureus can usually be isolated from the cellular debris Fairburn and Burgen described the probable sequence of events during the evolution of the cutaneous lesions. Migration of monocytic cells through the capillary wall occurs, or capillary hemorrhage may occur with the formation of small, local extravasation of blood cells The monocytic cells then proliferate in the perivascular region and extend to the dermal connective tissue, particularly in the sheaths of the hair follicles and sweat glands They believed, however, that in some cases the monocytic cells might originate from the histiocytes present in the blood vessels, sweat glands and hair follicle adventitiae Many of the small vessels become occluded by monocytic thrombi, the stroma undergoing an avascular hyaline change and later necrosis and ulceration It is probable, they stated, that the suppurative conditions develop as a result of the impairment of local defense mechanisms by monocytic infiltration Staphylococcus, as well as other organisms, which lie dormant in the hair follicles, are thus able to multiply freely with resulting infection

Case Report A 72 year old man first noted a 7 cm nodule on the hard palate This condition appeared to have originated on the palate and was followed, *several days later*, by generalized pruritus and intermittent headaches The following week numerous 1 cm cutaneous nodules appeared on the face, scalp trunk and extremities and, simultaneously the pruritus subsided Two to three weeks later the lesion on the hard pal...

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per cu mm Histologic examination of a nodular cutaneous lesion showed the entire dermis and superficial subcutaneous tissues to be markedly infiltrated by monocytic cells with patchy hyaline eosinophilic necrosis and ulceration The blood vessels were packed with monocytic cells Histologic study of a regressing furuncle showed dense invasion by monocytic cells, while only the hair follicles and sweat glands were invaded by these cells in the less markedly involved edge of the lesion Bone marrow studies revealed the sternal and femoral marrow to be extensively replaced by comparatively large and round, oval, or pyriform shaped monocytes The cytoplasm was ill-defined, the nucleus oval, reniform or lobular and finely granular, with occasional hyperchromatic bars There was a distinct nuclear membrane and a moderate number of mitoses were present, but there were no nucleoli The normal architecture of the spleen and lymph nodes was obliterated and they were diffusely infiltrated by monocytic cells, while the liver showed uniform necrosis of the central zones of the lobule, with a heavy peripheral infiltration The nodules which were present in the intestine were uniformly filled with monocytes The histologic picture, in all sections, was described *as showing an infiltration by cells of the monocytic* series with primitive and mature types in varying proportions In paraffin sections stained with hematoxylin and eosin these cells were at times indistinguishable from other cells of the lympho reticular series They were usually spheroidal pyriform or polygonal in shape and had an indistinct outline and lightly eosinophilic cytoplasm The nucleus was usually eccentric and relatively large showing various shapes from spheroidal to oval to reniform and finally band like often with a notched or lobulated appearance The chromatin was granular, and frequently a hyperchromatic longitudinal groove, an effect of the nuclear folding was present Nucleoli and mitoses were not prominent In the earlier lesions the infiltration was present between the connective tissue fibers and in the adventitia of the small vessels, but later the sebaceous and sweat glands and the hair follicles became involved There

2 per cent metamyelocytes and 1 per cent plasmacytes Sternal bone marrow studies disclosed a hyperplastic marrow with the normal marrow replaced by numerous early monocytic cells The histologic examination of a cutaneous lesion revealed sharply outlined nests of in filtrations which contained numerous monocytic cells, but mitotic figures were not found

D C Smith *et al* (638) reported a 58 year old man who presented numerous subcutaneous lesions, up to 10 mm in diameter, which were generalized but most marked on the back, chest and abdomen These rounded, reddish purple le sions were slightly raised, smooth and infiltrated Histologic study of a cutaneous nodule from the abdomen showed dif-fuse infiltration of the superficial portion of the corium with large cells having some degree of pleomorphism The nuclei were oval or round to notched and kidney shaped, and there were occasional mitoses The cells showed a wide zone of cytoplasm with indefinite boundaries, nucleoli were prominent in some cells and a fine reticulum partly replaced the larger collagenous fibers in this area This picture was believed to be compatible with cutaneous monocytic reticulosis The pa-tient s condition continued to decline, the peripheral white blood cells never exceeded 600 per cu mm and although many of the cutaneous lesions had resolved, numerous pete-chiae and ecchymoses developed A 57 year old man who presented numerous nodules and plaque like cutaneous le-sions, up to 4 cms in size, was reported by Mann (424) The lesions were most numerous on the face, neck and left fore-arm and some were infected and excoriated "exposing pink deposits of leukemic tissue beneath the cutis"

It was the opinion of Montgomery and Watkins (459c) that there is no essential difference between the cutaneous manifestations present in the Schilling and Naegeli types of monocytic leukemia They described two cases of monocytic leukemia (Schilling) associated with cutaneous manifesta-tions The first patient was a 45 year old man who had a cutaneous eruption ("eczema") which began on the legs six

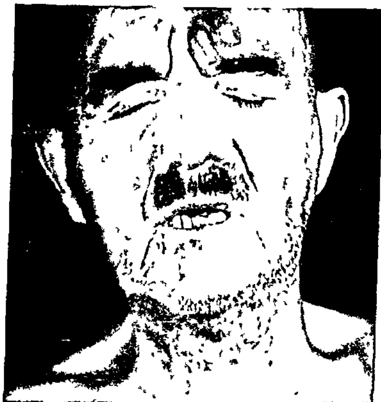


Figure 46 Cutaneous nodules on the face (case report) (*A M A Arch Dermat* 73 189, 1956)

cm , nonulcerated nodule developed on the left side of the forehead over the eye There was a generalized cutaneous eruption consisting of 1 cm , violaceous to light brown nodules The prostate was enlarged and there was moderate generalized lymphadenopathy The hemogram revealed 71 per cent hemoglobin, 3,760 000 red blood cells and 4,900 white blood cells per cu mm , with 68 per cent polymorphonuclears, 19 per cent lymphocytes, 9 per cent monocytes, 1 per cent basophils and 2 per cent metamyelocytes Ten days later the hemogram showed 80 per cent hemoglobin, 3,990,000 red blood cells and 2,950 white blood cells per cu mm , with 20 per cent polymorphonuclears, 40 per cent lymphocytes, 35 per cent monocytes 2 per cent eosinophils,

definite granulocytic immaturity back to the stem cell, and a marked predominance of monocytic cells The diagnosis was monocytic leukemia (Naegeli) One month later, small nodular cutaneous lesions involved the right foot and the anterior surfaces of both legs These lesions showed a "definitely lymphoblastomatous picture," on histologic examination with many large immature cells and monocytes This case was one of typical monocytic leukemia (Naegeli) which evidenced discrete specific cutaneous nodules in the terminal stage of the disease These nodules are frequently present in leukemia, particularly with lymphocytic leukemia but are rarely present with granulocytic leukemia There was no characteristic clinical picture in these cutaneous nodules Montgomery and Watkins concluded that a distinction is made between the Naegeli and Schilling types of monocytic leukemia on the hemocytologic picture and either type may be of autochthonous cutaneous origin The cutaneous lesions present in either type may be specific or nonspecific, and may vary from discrete necrotic nodules or purpuric lesions to generalized exfoliative dermatitis The distinctive histopathologic picture of monocytic leukemia (Schilling) is present when the histologic findings of the cutaneous lesions correspond with the hematocytologic picture

Degos et al (143d) believed that the frequency of cutaneous manifestations in monocytic leukemia could be due to the large amount of reticular and histioid tissue in the skin They described a 70 year old man (case 1) whose only symptoms for one month were small, purplish, widely disseminated cutaneous nodules Splenomegaly and lymphadenopathy then developed and his general health began to deteriorate Histologic study of a cutaneous nodule revealed infiltration of the dermis and hypoderm by abnormal reticular cells which were essentially monocytes The same changes, although less marked were also present in apparently uninvolved cutaneous areas The first hemogram was "almost normal" but later studies revealed 56 per cent monocytes The sternal bone marrow showed 56 per cent large abnormal cells, interpreted

weeks previously and soon became generalized Histologic studies of a lesion revealed a dense infiltration of reticulum cells "and other features of lymphoblastoma," although the type could not be determined High voltage roentgenotherapy was administered to the neck, mediastinum, groin, back, and pelvis The following year the cutaneous plaques had become more infiltrated and the clinical picture was "more suggestive of mycosis fungoides" The histologic picture was still not specific for a particular type of lymphoma and roentgenotherapy was again administered Three years later he had two cutaneous plaques in the left pectoral region and one on the left forearm and some of the nodules had become infiltrated and ulcerated Histologic studies now revealed a more active process with numerous mitotic figures The diagnosis of "mycosis fungoides bordering on lymphosarcoma" was considered and further roentgenotherapy was given Five months later the cutaneous lesions were greatly improved However, the hematocytologic picture showed marked poikilocytosis with marked basophilic stippling, 'occasional normoblasts and definite immaturity in the myeloid line back to the myeloblast or stem cell with predominant differentiation along the monocytic line The diagnosis of monocytic leukemia was suggested A short time later the hemogram showed the monocytes to be more predominant and immature They were in all stages of development from the monoblast to the stem cell The diagnosis of monocytic leukemia (Naegeli) was then established and this diagnosis was confirmed at autopsy one month later Their second patient was a 51 year old man who had cervical lymphadenopathy of six weeks duration He presented hypertrophy of the gums and mucous membranes of the mouth and soft palate, which was also swollen and edematous All cervical lymph nodes were enlarged and the spleen and liver were palpable He had paralysis of the left side of the face and a 'fading purpuric eruption" involving the legs and thighs, but there was no infiltration suggestive of leukamids Hematocytologic studies revealed marked poikilocytosis with marked basophilic stippling increased regenerative activity,

myelocytes 34 per cent lymphocytes, 5 per cent monocytes, and 14 per cent "histiomonocytic" types Histologic study of the lymph nodes showed 41 per cent "abnormal nucleated reticular cells," 39 per cent "shriveled" lymphocytes, 10 per cent prolymphocytes, and 10 per cent lymphoblasts The histologic examination of the skin showed "histiomonocytic" hyperplasia with some lymphocytic infiltration There was clinical improvement of the cutaneous lesions following roentgenotherapy and the peripheral blood showed suppression of lymphocytic cells and stimulation of monocytic cells one count revealed 60 per cent monocytes The cutaneous lesions recurred and he died four months later This case is an example of "lymphomonocytic leukemia," according to Degos *et al* The alternate discharge of lymphocytes and monocytes, and histiomonocytic hyperplasia of the skin, with some lymphocytes, indicated two parallel malignant processes one histiomonocytic, the other lymphocytic.

F. "Aleukemic" Reticuloendotheliosis

There are numerous reports concerning the association of hyperplasia of the reticuloendothelium with the formation of monocytes Hyperplasia of the reticuloendothelium is frequently associated with excessive peripheral blood monocytosis Hyperplasia of the reticulum has been compared with systemic hyperplasias of lymphopoietic and myeloplastic tissues Distinction is made between "aleukemic" and leukemic reticuloendotheliosis If this assumption is correct, leukemic reticuloendotheliosis would be identical to monocytic leukemia

"Aleukemic" reticuloendotheliosis was described by F W Lynch (409a) as an acute or chronic condition In the acute form the clinical course is characterized by a sudden onset, fever, necrotic angina, and a hemorrhagic diathesis, symptoms corresponding to those which occur in other types of acute leukemia "which recall Sternberg's opinion that acute leukemia is the result of sepsis" Bacterial organisms have been observed in a few cases but they usually are not demonstrable

as "hemocytoblastic or reticular cells" A hectic fever, loss of weight and weakness then occurred and he died one month later Although some investigators would consider this case to be one of monoblastic leukemia (Naegeli), Degos *et al* believed that a "reactional' cutaneous process, secondary to monoblastic or "hemocytoblastic' leukemia, would scarcely produce such *severe disturbance in the reticular series* Also, the cutaneous lesions preceded invasion of the blood by monocytic cells In their opinion these facts would support the diagnosis of malignant reticuloendotheliosis with monocytic leukemia (Schilling)

Another patient described by Degos *et al* (case 2) was a 40 year old woman who *first had lesions on the mucous membranes of the pharynx* which progressed to the buccal and lingual mucosa and were followed by an ulcerated, vegetative *lesion on the lower lip There were 67 per cent typical monocytes* in the peripheral blood and the myelogram showed 73 per cent basophilic cells The diagnosis was 'monoblastic *and monocytic' leukemia The mucous membrane lesions regressed* and the anemia disappeared following transfusions of whole blood and the administration of cortisone and anti*biotics However the monocytes persisted in the peripheral* blood and the bone marrow became more monoblastic. According to Degos *et al* this case *exemplified the most authentic (Naegeli) type of monocytic leukemia While the ab*normal peripheral blood cells were typical monocytes, the bone marrow cells appeared to be both monoblastic and reticular *Mucosal lesions are perhaps more typical in this type of* leukemia

Degos *et al* reported another patient (case 4), a 74 year old man, who presented *a slowly progressive cutaneous eruption* of erythematous, vesicular, oozing plaques which were somewhat infiltrated and markedly pruritic There were hard, painless *inguinal and axillary lymph nodes The hemogram* revealed 4,030,000 red blood cells and 58,400 white blood cells per cu mm, with 70 per cent lymphocytes and 10 per cent monocytes *The bone marrow showed 30 per cent neutrophilic*

bled immature mesenchymal cells New buccopharyngeal lesions accompanied by fever continued to appear and although the ulcers healed the lymphadenopathy increased and formed an inflammatory reaction On histologic examination the nodules were found to be composed of monocytic cells having voluminous reticulocytic elements and foci of central necrosis surrounding the blood vessels sweat glands and pilo sebaceous follicles

A patient in whom predominant cutaneous symptoms appeared *two months* before death was described by Weidman and Custer (715a) These lesions were for the most part grey white intracutaneous nodules involving the cheeks breasts arms legs and inner aspects of the thighs There was one nodule at the corner of the mouth and others could be palpated in the fascia of the abdominal wall These nodules later assumed a bluish color and subsequently developed into small plaques or diffuse layers There was moderate generalized lymphadenopathy and the peripheral white blood cells reached 400 000 per cu mm The diagnosis of acute leukemic reticuloendotheliosis (monocytic leukemia) was confirmed at autopsy

A 60 year old man who had infiltrated nonpruriginous nodules on the back scalp and upper extremities which appeared five months previously was described by Craps *et al* (129) Histologic examination of the scalp nodule suggested "mycosis fungoides" but the other lesions indicated "Hodgkin s disease" There was preauricular and submaxillary lymphadenopathy Histologic study revealed newly formed cells

and there were 5 per cent

A diagnosis of acute histio-monocytic leukemia was then made which was "verified by the cell count in the bone marrow " Symptoms of generalized septicemia general malaise and temperature to 104 deg F followed the second injection of chloroethylamine The cutaneous lesions increased rapidly in size and he died from "severe visceral generalization" one month after admission to the hospital

Therefore, most investigators believe these organisms are the result of secondary invasion He described chronic "aleukemic" reticuloendothelial proliferation as a condition which is difficult to distinguish from hyperplasia secondary to chronic infectious processes or *from lymphogranulomatosis,* both clinically and pathologically The atypical forms of these diseases may present an extremely confusing symptomatology and pathology Despite the confusion regarding the proper diagnosis of these cases, Lynch believed that some represented a group generally considered to be "chronic aleukemic reticuloendotheliosis" which may "well be called aleukemic mono cytic leukemia" The cutaneous lesions are very similar to those of leukemia In the acute form, macular or papular eruptions which develop into nodular lesions may occur These lesions tend to become hemorrhagic, necrotic or distinctly pustular

According *to Tasei et al (675), this more frequent form* of the disease is either fatal within a few months time or it develops slowly, after a fulminating onset, in which case the cutaneous manifestations usually precede the terminal stage of the disease They described a 28 year old man who first had dysphagia, arthralgia and anesthesia of the skin, buccopharyngeal ulcers and lymphadenopathy He had several remissions and exacerbations of these symptoms for three years before the cutaneous lesions became pronounced On examination, necrotic cutaneous lesions had been apparent for several months and the buccopharyngeal mucosa was covered with small white ulcers which were surrounded by an erythematous areola There was marked hepatosplenomegaly, as well as a large area of cutaneous ulceration on the cheek and upper portion of the neck which was indurated and ulcerated, the largest lesion being 8 by 4 cms in size The region surrounding the ulcers was edematous New large, black areas, which appeared to result from coalescence of smaller lesions, were present in the subdeltoid region Histologic study of the edge of an ulcer showed markedly inflamed connective tissue with polymorphonuclear infiltration and large cells which resem-

which was believed to be partly of nutritional origin Marked superficial lymphadenopathy involved the cervical, axillary and inguinal regions These lymph nodes were firm, nontender and usually discrete, except for some matting in the right axillary and inguinal regions There were pinkish grey tumors in both nasal cavities which caused the nose to appear broadened The tonsils were firm and enlarged The cutaneous surface was atrophic, with numerous sharply circumscribed, raised, firm dull red 4 mm to 2 cm cutaneous nodules and tumors involving the face, back and extensor surfaces of the extremities These painless freely movable lesions showed no tendency toward grouping The skin covering the tumors was smooth shiny, and intact, with telangiectasia at the periphery of the lesion Marked fusiform swelling and small superficial nodules were present on several fingers The pathologic diagnoses, at autopsy, were "aleukemic reticuloendotheliosis" of the skin lymph nodes, bone marrow, pancreas, thyroid gland, lungs, stomach nasal mucosa, and tonsils On histologic examination the cutaneous nodules were of a greyish white color and usually extended into the corium and subcutaneous tissue There were diffuse masses of loosely arranged, discrete, large, round monocytic cells which showed little variation in size and shape

Pautrier (509a) reported a 37 year old man who had a nearly generalized cutaneous eruption of soft, red brown, partly ulcerated tumors which clinically resembled mycosis fungoides However, on histologic examination of a tumor there were lymphocytes, and cells not readily identifiable which resembled young histiocytes He had a tumor inside the nose, an ulcer of the epiglottis and tuberculosis of the pulmonary apices The blood picture was not characteristic of leukemia and "aleukemic" leukemia also did not seem a plausible diagnosis It was Pautrier's opinion that this case was another of the group called "unclassifiable granulomatosis,' a term which he had introduced in 1937

A patient described by Montgomery and Watkins (459c case 3) presented autochthonous origin of the disease Although the lesions first simulated mycosis fungoides, they later developed into an exfoliative dermatitis They believed this case to be the first report of exfoliative dermatitis associated with monocytic leukemia (Schilling) There were a few "grooved cells" present in the cutaneous histologic section and, one year later, "peculiar, grooved and serrated, immature" monocytic cells were found in a cutaneous lesion and in the peripheral blood smears In this case, and in another (case 1) they described, the early cutaneous histopathologic picture resembled that of mycosis fungoides Wayson and Weidman (712) also described a patient with monocytic leukemia who had cutaneous lesions which *simulated those of mycosis fungoides*

Freeman and Koletsky (199) described a 48 year old woman who had several firm cutaneous and subcutaneous nodules and tumors involving the face, lower extremities and right upper extremity Subsequently she presented numerous 0 5 to 1 5 cm, painless, elevated, purplish red nodules on the arms, legs and back Histologic study of three cutaneous lesions were reported to show lymphoblastoma, probably of reticuloendothelial type" She became emaciated and pale and pitting edema of both legs and of the right arm developed, as well as hydrothorax, ascites and severe anemia,



Figure 47 Peripheral blood smear showing an increased number of plasmacytes

Figure 48 A typical plasmacyte

VI

PLASMACYTIC LEUKEMIA

(MULTIPLE MYELOMA)

PLASMACYTIC LEUKEMIA is characterized by either a focal or a diffuse abnormal overgrowth of plasmacytes and occurs predominantly in individuals from 40 to 70 years of age

The clinical features of this disease, other than cutaneous, are (1) pain in the bones, (2) pathologic fracture, (3) neurologic manifestations, (4) gastrointestinal symptoms, (5) fever, (6) splenomegaly and hepatomegaly, (7) lymphadenopathy, (8) extramedullary lesions, (9) abnormalities of bone demonstrable by roentgenograms, (10) kidney abnormalities, and (11) pulmonary involvement

The characteristic cells which are present in the relatively benign, chronic, multiple myelomas are the "typical" plasmacytes, according to Campbell and Good (95) These cells are characterized by four simultaneous structural features (1) Heavy plaque like chromatin aggregations in the nucleus, with sharp boundaries (in contradistinction to the chromatin clumps present in lymphocytes) which account for the well-known "cartwheel nucleus, (2) intense basophilia of the cytoplasm, (3) the presence of a clear space in the nucleus, usually in the widest part of the cytoplasm, and (4) a decided eccentricity of the nucleus The more acute forms of myeloma are characterized by primitive cells having no characteristic differentiation but rather by a tendency to syncytial arrangement and a definite resemblance to primitive endothelial cells, according to S O Schwartz (615a)



Figure 47 Peripheral blood smear, showing an increased number of plasmacytes

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Figure 50 Pathologic fracture due to myeloma of the bone

macytic myeloma depends upon the finding of an increased number of large immature plasmacytes in the bone marrow Other pertinent laboratory findings are Bence Jones proteinuria and hypercalcemia with a normal alkaline phosphatase

A. Cutaneous Manifestations of Plasmacytic Leukemia

- I Specific
  - A Extramedullary Plasmacytomas
    - 1 Skin
    - 2 Mucous membrane
  - B Cutaneous Tumors (Extension from Involvement of the Bone)
- II Nonspecific

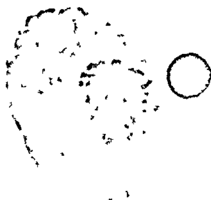


Figure 49 A plasmacyte undergoing mitosis

The origin of the plasmacyte is by no means clear Most investigators believe that the reticulum cell is the precursor of the plasmacyte The results of our studies (Rostenberg, Jr and Bluefarb, 582) would appear to support this theory, since there was involvement of the reticuloendothelial system However, there is a considerable amount of evidence regarding a close immunologic relationship between plasmacytes and lymphocytes

The roentgenographic changes are characteristic in most cases of multiple myeloma The bone changes, especially of the skull, reveal characteristic rounded, punched-out areas having sharp margins, but there is no evidence of surrounding osteoblastic reaction Meacham (442) believed that diffuse osteoporosis is a common finding in multiple myeloma

The important hematologic findings consist of (1) anemia, (2) excessive rouleaux formation, (3) immaturity of both the red and white blood cells (4) presence of atypical and typical plasmacytes, (5) lymphocytosis and eosinophilia, and (6) elevated sedimentation rate The ultimate diagnosis of plas-

2 Lungs
   a Disappearance of lunulae from base of nails
   b Clubbing of fingers
3 Nerves and ganglions
   a Herpes zoster (due to pressure of ganglion from extension of bone tumor)

plasmacytoma of the bone marrow These tumors have a predilection for the upper respiratory passages but may involve the stomach, intestines pancreas, pleurae, thyroid gland, urogenital tract and skin Bence Jones proteinuria has never been reported in cases of extramedullary plasmacytoma without skeletal involvement, according to Snapper *et al* (642)

The two main hypotheses concerning the pathogenesis of extramedullary lesions of multiple myeloma are autochthonous growth (Lubarsch 401) and direct transmission of myeloma cells It is postulated that since hematopoiesis can occur outside the bone marrow, proliferations of myeloma cells can also occur *in situ* Because myeloma cells appear to arise from the reticuloendothelial cell it appears likely that the extramedullary lesions in organs containing such reticuloendothelial tissue arise from this tissue rather than by metastases

The first case report of extramedullary plasmacytoma involving the skin was that of Bruno Bloch (53) in 1910 His patient a 67 year old man had lesions on the extremities and chest which began as erythematous macules, and then became papules with scales and crusts Autopsy revealed multiple myeloma with metastatic lesions Hayes *et al* (261) reported a patient in whom a tumor of the pancreas was found at autopsy Histologic examination of a cutaneous nodule, which had been removed during life, revealed cells identical to those found at autopsy Kreibich (335a) described a 78 year old man who had cutaneous nodules on the face MacLeod's (419a) patient, a 35 year old woman, presented a slightly

- A Cutaneous Manifestations Due to Abnormal Proteins
  - 1 Amyloid
    - a Macroglossia
    - b Papules and nodules
    - c Purpura
    - d Alopecia
  - 2 Cryoglobulins
    - a Raynaud's disease
    - b Ulcers and necrosis of the skin
    - c Purpura
    - d Cold urticaria
    - e *Cutis marmorata*
  - 3 Elevated serum globulins
    - a False positive blood serologic test
    - b Poor immunologic response
- B Cutaneous Manifestations Due to Cytopenias
  - 1 Anemia
    - a Glossitis
    - b Pallor
    - c Koilonychia
  - 2 Leukopenia
    - a Pyoderma
    - b Agranulocytic membrane
  - 3 Thrombocytopenia
    - a *Hemorrhagic tendency*
- C Toxic Cutaneous Lesions
  - 1 Erythemas and pigmentations
  - 2 Alopecia
  - 3 Icthyosiform atrophy of the skin
  - 4 Seborrhea-like dermatitis of the face
- *D Cutaneous Manifestations Due to Myelomatous* Involvement of Internal Organs
  - 1 Kidneys
    - a Pruritus
    - b Pitting edema
    - c Uremic frost

2. Lungs
   a Disappearance of lunulae from base of nails
   b Clubbing of fingers
3 Nerves and ganglions
   a Herpes zoster (due to pressure of ganglion from extension of bone tumor)

I. Extramedullary Plasmacytoma. Extramedullary plasmacytic tumors are comparatively rare, although Hellwig (274) collected many cases which were histologically identical with plasmacytoma of the bone marrow These tumors have a predilection for the upper respiratory passages but may involve the stomach, intestines, pancreas, pleurae, thyroid gland, urogenital tract and skin Bence Jones proteinuria has never been reported in cases of extramedullary plasmacytoma without skeletal involvement, according to Snapper *et al* (642).

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down to the forehead in front with elongated thickened pro cesses in front of the ears down to the nape

Extramedullary tumors have a predilection for the mucous membranes especially the upper part of the respiratory tract According to Lewis *et al* (389) the diagnosis of extramedullary plasmacytic tumors can be made only by histologic examination because of the tremendous variation in the clinical picture In the upper respiratory passages these tumors may be polypoid pedunculated or sessile they may appear as simple enlargements or diffuse swellings of the mucous membranes The color has been variously described as bluish red yellowish grey and sometimes dark brown Noninvasive extramedullary tumors or those with only lymph node metastases are usually of firm consistency Lewis *et al* described a 59 year old man who had an asymptomatic tumor of the left nostril This lesion was firm cylindrical flesh colored and attached to the mucosal surface of the left ala nasi 2 mm from the naris The surface of the lesion was slightly verrucous and the walls smooth It measured about 5 mm in length and projected outward through the left naris A patient described by Jackson *et al* (311) had a plasmacytoma of the left tonsil which was removed by surgery Two years later a similar lesion developed on the right tonsil Seven years after the appearance of the initial lesion all the signs of classic myeloma were present

2 *Tumors of the Skin (Extension from Involvement of the Bone)* Locally invasive tumors and those associated with metastases to the bone are usually soft and may be partly necrotic or ulcerated The cutaneous tumors of multiple myeloma are usually described as being ulcerated nodules resembling the "d emblee" type of mycosis fungoides (lymphosarcoma) Occasionally the nodules in the skull appear as "soft spots" and on palpation feel like a lipoma or sebaceous cyst, as illustrated in one of our patients

Duvoir *et al* (157) reported a 59 year old man in whom the disease began as a spontaneous fracture of the left arm One year later multiple raised nodular infiltrated lesions ap

raised, circular, bluish-black, pigmented "patch," about 2 cms in diameter, on the posterior fold of the left axilla. There was no axillary lymphadenopathy. The lesion suggested melanotic carcinoma clinically, but histologic examination disclosed myeloma.

Nicholls (478) reported a 74 year old woman who had numerous small sessile cutaneous nodules which were slightly elevated and appeared "rather pearly" and were surrounded by a reddish-brown areola. These lesions were present around the waist and followed the course of the diaphragmatic attachment. Newns and Edwards (477) described a 42 year old woman who had subcutaneous nodules on the wall of the chest, scalp, and median margins of the left orbit. Histologic examination of a lesion from the chest revealed a mass of plasmacytes with a scanty fibrous matrix supporting the capillaries. The diagnosis of "plasmacytoma" by histologic examination of the subcutaneous tumor, the presence of a large metastatic deposit in one kidney, and the demonstration of widespread renal tubular obstruction, were believed to be an "unusual finding." A cutaneous tumor of the neck which occurred in a six year old girl, reported by Aragona (12), was found to be composed of plasmacytes. The lesion had not recurred five years after it was excised. Switzer *et al* (668) described a 58 year old Negro who had various sized tumors which were most numerous on the face and scalp, but also involved the head, trunk, right leg and scrotum. These pink colored, nontender, soft, pedunculated tumors bled readily after trauma and varied from 0.1 to 3.0 cms in diameter. A nodular mass on the anterior right pillar resembled the cutaneous nodules.

Piney and Raich (524b) described a 56 year old man who first had a 'lump' on the forehead which grew rapidly in size. He had diffuse nodular cutaneous lesions over the trunk and extremities which clinically resembled neurofibromatosis. The peripheral white blood cells numbered 42,500 per cu mm, with 33.5 per cent plasmacytes. At autopsy the scalp was markedly thickened, a peculiar "helmet like" shape extended

had numerous subcutaneous nodules which appeared several weeks before her death Autopsy revealed extensive plasmacytic infiltration of the viscera Hedinger (271) described an "unusual" tumor of the scalp On histologic study, one-half of the tumor was found to be composed of plasmacytes and the other half was apparently an adenocarcinoma originating in a sweat gland The cervical lymph nodes showed only metastatic carcinoma

Among 88 cases of multiple myeloma at the Cook County Hospital (Chicago), nine presented cutaneous tumors which were extensions from myelomatous involvement of the bone These cases were described by Bluefarb (56d)

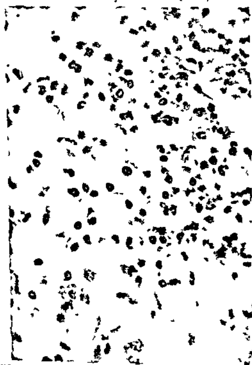


Figure 52 Histologic section showing marked increase of plasmacytes (A M A *Arch Dermat* 72 506 1955)

peared They were scattered over the scalp arm and clavicular region The nodule on the extensor surface of the forearm was round umbilicated and composed of many lobules some of which were firm in consistency others soft and of a "raspberry" color This nodule simulated a mycosis fungoides like tumor Kin (341) described a similar case in which the nodular infiltrations over the face and back were large umbilicated and ulcerated presenting the clinical picture of mycosis fungoides Christian (113a case 6) described a 54 year old man who had a small tumor in the sternal region at about the level of the nipples which had been present for one year This rounded tumor had steadily increased in size and was about 11 cm in diameter rather soft and slightly pulsating There were several nodules on the ribs Roentgenograms showed changes in the left fifth sixth seventh eighth eleventh and twelfth ribs posteriorly and in the seventh and eighth ribs on the right side Snapper *et al* (642) described a woman who



Figure 51 Metastatic tumor of multiple myeloma (*A M A Arch Dermat* 72 506 1955)

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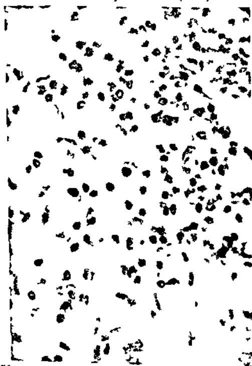


Figure 52 Histologic section showing marked increase of plasmacytes (*A M A Arch Dermat* 72 506 1955)

The first patient was a 58 year old Negro who complained of constipation joint pains "tumor" of the chest and a loss of 50 pounds in weight He was unable to work because of severe pain which first occurred in the region of the hip and later in the spine There was a large tumor with central ulceration involving the left side of the chest The peripheral blood count was reported to be normal Examination of the sternal bone marrow revealed a predominance of plasmacytes compatible with the picture of multiple myeloma Histologic examination of the tumor showed plasmacytic myeloma Roentgenograms of the pelvis and skull showed myelomatous involvement and destruction of the fifth rib Biochemical studies revealed total protein 9 8 mg /100 cc albumin 3 4 gm /100 cc globulin 6 5 gm /100 cc and gamma globulin 3 04 gm /100 cc

Another patient a 38 year old man complained of pain in the ribs thighs and back Examination revealed hard raised



Figure 53 Myelomatous involvement of the skull (*A M A Arch Dermat* 72 506 1955)

nodules over the sternal area Roentgenograms revealed lesions of the skull and pelvis which were suggestive of multiple myeloma The sternal bone marrow showed an increase of plasmacytes compatible with a diagnosis of multiple myeloma

C

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clinically was present on the scalp Examination of material aspirated from this lesion showed numerous plasmacytes The blood count was reported to be normal The sternal bone marrow examination disclosed the findings present in multiple myeloma

3 *Cutaneous Manifestations Due to Abnormal Proteins* The



Figure 54 Myelomatous involvement of the fifth rib (*A M A Arch Dermat* 72 506 1955)



Figure 55 Myelomatous nodule of the scalp resembling a sebaceous cyst

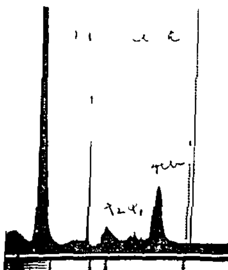


Figure 56 Abnormal peak of the gamma globulin

plasmacyte apparently produces a variety of abnormal globulins The most frequent finding in the electrophoretic pattern is an abnormal peak in the gamma globulin and in rare cases the alpha globulin is increased It has been noted that an increase in alpha globulin is associated with more mature cells and a less malignant course (Wuhrmann *et al* 745) Patterns with tall narrow peaks in the beta regions in the gamma region or intermediate between the gamma and beta regions are virtually characteristic of multiple myeloma (S O Schwartz 615a)

a AMYLOIDOSIS Primary systematized amyloidosis is of particular interest because it may be associated with myelomatosis Although the occurrence of amyloidosis as a complication of plasmacytic myeloma has long been recognized the incidence is probably low Among our (56d) 88 patients amyloidosis was present in only five cases

One patient was a 67 year old Mexican man who complained of bleeding hemorrhoids and a weight loss of 15 pounds during the preceding two months He presented nodules on the upper portion of the gum and tongue Histologic examination of the lesion on the tongue revealed amyloidosis The peripheral blood count was reported to be normal and the sternal bone marrow revealed sheets of plasmacytes characteristic of multiple myeloma

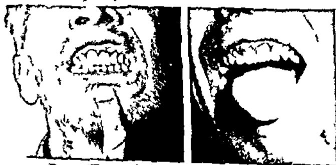


Figure 57 Amyloid nodules of upper gum
Figure 58 Amyloid nodules on tongue of patient in Figure 57 (A M A *Arch Dermat* 72 506 1955)

Figure 59 Histologic section showing deposition of amyloid on tongue (*A M A Arch Dermat* 72 506 1955)



Figure 60 Macroglossia due to amyloid infiltration (*A M A Arch Dermat* 72 506 1955)



Figure 61 Unilateral gynecomastia (*A M A Arch Dermat*, 72 506 1955)

Another patient was a 49 year old Negro who presented slight redness and enlargement of the tongue and pretibial edema with ichthyosiform atrophy of the skin of the lower extremities Purpura then appeared on the upper anterior chest wall Complete hematologic studies including sternal bone marrow examination gave normal results Autopsy revealed a primary systematized amyloidosis associated with multiple myeloma

A 45 year old man who had multiple myeloma confirmed by sternal bone marrow examination also presented a unilateral gynecomastia Histologic study of tissue of the gynecomastia revealed infiltration with amyloidosis

Wells (720) gave the diagnostic criteria of primary systematized amyloidosis as follows (1) There is no chronic suppuration granulomatous disease or rheumatoid arthritis as in secondary amyloidosis (2) the distribution of the amyloid is distinctive with widespread involvement of muscle and small blood vessels Particular features are amyloid macroglossia gastrointestinal and cutaneous infiltration and heart failure and (3) metachromatic staining for this kind of amyloid is variable

Figure 59 Histologic section showing deposition of amyloid on tongue (*A M A Arch Dermat* 72 506 1955)

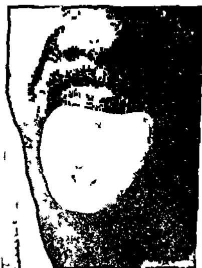


Figure 60 Macroglossia due to amyloid infiltration (*A M A Arch Dermat* 72 506 1955)

paramyloid deposition One of Snappers patients had no grossly visible lesions on the tongue or mucous membranes of the mouth but histologic examination of the tissue during life showed extensive amyloid infiltration of the submucous layers and especially of the muscular coats of the blood vessels Probably if more histologic studies of the gingivae were done as advocated by Selikoff and Robitzek (622) this incidence would be much higher They also stated that amyloid is characteristically more abundant in perivascular areas and amyloid substance may be found wherever there are blood vessels It is this latter fact which makes the gingivae a particularly likely site in which to find amyloid deposits since the gum like most tissue in the oral cavity is highly vascular Michelson and Lynch (445) obtained material for histologic study from the skin and mucous membranes and observed that the mucous membranes are an excellent site in which to demonstrate amyloid The gingivae which are easily accessible contain few pain nerve endings and are also remarkably resistant to infection Since this disease affects an older age group many of these patients are edentulous These are all attributes which make histologic studies of tissue from this region practical

Brunsting and MacDonald (80) described four *cases of* primary systematized amyloidosis associated with macroglossia Macroglossia was a presenting sign in three *patients and* developed late in the course of the disease in the fourth patient The tongue was enlarged from one to two times the normal size and in one case it protruded 2 5 cms out of the *mouth during sleep Impairments* of speech and swallowing were consistently present

In a comprehensive review of the symptomatology and
loidosis Koletsky and
prior to 1929 which
h (401) They added
an illustrative case *in* which the disease was of 14 years duration the longest recorded *They found* the organs most frequently involved to be the tongue heart, stomach intes

The four basic etiologic theories in the causation of amyloidosis were listed by Mathews (437) as (1) Amyloid disease is a manifestation of a disturbance in general or localized protein metabolism (2) it is the result of an antigen antibody reaction and precipitation in the tissues (3) amyloidosis is the result of an abnormality or disturbance in the reticulo endothelial system and (4) amyloidosis is related to hyper globulinemia

Snapper *et al* (642) described the primary systematized amyloidosis as paramyloidosis" Not only is paramyloidosis associated with multiple myeloma but in addition it has been associated with ingestion of drugs (Teilum 676 Robertson 567) trichinosis and systemic lupus erythematosus (*Teilum 676*) In primary amyloidosis or paramyloidosis the deposition occurs in atypical locations mainly in the mesodermal tissues of the heart blood vessels gastrointestinal tract and skin In the secondary amyloidosis which follows prolonged suppuration the localization of the amyloid is predominantly in the liver spleen kidneys adrenal glands and walls of the blood vessels

There is frequently involvement of the tongue in systemic amyloidosis This ranges from a microscopic involvement of the blood vessels to a massive replacement of the musculature by diffuse or nodular masses of amyloid apparently formed in the interstitial tissues and replacing the muscle bundles by compression and atrophy This produces a diffuse symmetrical enlargement of the tongue and marked rigidity or induration of the tongue visible as the characteristic translucent grey patches streaks or nodules The surface of the tongue is variously described as smooth pale and atrophic or with red papules protruding on the surface The macroglossia may become so marked that the tongue *fills the entire mouth* Superficial ulcerations occur infrequently

In a series of 11 cases complicated by amyloid which were reported by Snapper *et al* (642) two patients had deposits in the skin and four in the tongue Only three patients in Bluefarb s (56d) series demonstrated macroglossia due to

eyebrow, axillary, and pubic hair was sparse The scalp hair was diffusely thinned and appeared dry and "lifeless" In the axillae there was no apparent thickening of the skin, but in the pubic area the skin was apparently heavily and diffusely infiltrated with amyloid Lubarsch (401) also described loss of hair in one patient

Bluefarb *et al* (56k) presented a 56 year old man who had primary systematized amyloidosis associated with multiple myeloma There were small raised, firm shiny, cutaneous



Figure 62 Amyloidosis of the forearms



Figure 63 Amyloidosis behind the ear

Figure 64 Amyloid nodule in ear canal

tine, and skeletal muscles Of these 24 patients, eight had cutaneous involvement and 20 had involvement of the tongue, while swelling of the tongue was a prominent symptom in 13 of 20 patients Parkes-Weber *et al* (502f) emphasized the frequent occurrence of macroglossia in amyloidosis They reviewed 10 such cases and reported an additional one

Estimates of the frequency of amyloid deposits in multiple myeloma vary considerably from 6 to 25 per cent This reflects the varying degrees of clinical awareness and the difficulties encountered in its recognition during life A reasonable average is probably about 15 per cent (Bayrd and Bennett 33)

The cutaneous manifestations of amyloidosis are described as waxy yellow, indurated, opalescent, spherical, flat topped papules or nodules, or a pseudoscleroderma Lesions on the eyelids have been mistaken for xanthelasma Goltz (234) stated that the most striking and characteristic cutaneous lesions are the translucent papules and plaques The most common sites of involvement are the eyelids, nasolabial commissures, cleft of the chin, sides of the neck, and the axillary, inguinal and anal regions His second patient had, in addition to a diffuse thickening of the scalp, groups of nodules and tumors in the nape, scalp and anogenital areas Brunsting and MacDonald (80) described small shot like indurations and small nodules present on the palms Rigdon s (563) patient had several small firm, freely movable nodules in the posterior region of the scalp

Purpura is a frequent manifestation of amyloid disease and may be an initial symptom The hemorrhages may occur on any cutaneous surface and may appear on apparently normal skin or in areas having amyloid infiltration Purpura is apparently caused by damage to the walls of the cutaneous and mucosal blood vessels from infiltration by amyloid

One of the patients described by Snapper *et al* (642) presented an almost total alopecia due to amyloid infiltration of the subcutaneous tissues of the scalp The loss of hair was a striking feature in Goltz's (234) second patient The scalp,



Figure 66 Osteolytic lesions of the skull

ulin were present Hemogram revealed 52 per cent hemoglobin 2 750 000 red blood cells and 5 700 white blood cells per cu mm with 44 per cent polymorphonuclears 43 per cent lymphocytes 6 per cent basophils 4 per cent monocytes and 3 per cent eosinophils as well as "considerable anisocytosis poikilocytosis and polychromatophilia" The sternal bone marrow was completely infiltrated with sheaths of mature plasmacytes The findings indicated multiple myeloma Biochemical studies were normal except for 12 5 mg /100 cc calcium and the protein electrophoresis (serum) showed increased alpha 2 decreased gamma Electrocardiograms indicated a first degree heart block The venous pressure was elevated with prolonged arm to lung circulation time and normal arm to tongue circulation This was reported to indicate "right heart failure such as occurs in amyloidosis of the heart" Following the administration of P32 there was no marked retardation of the disease process Histologic studies

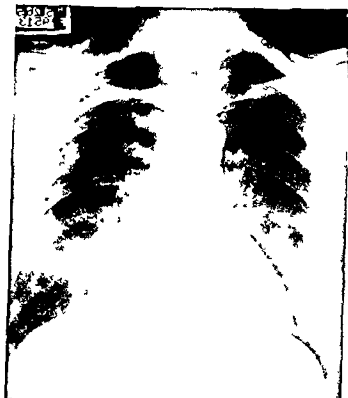


Figure 65 Osteolytic lesions of the ribs

papules on the dorsum of the hands which had appeared six months previously Two weeks later similar lesions appeared on the forehead and back of the neck which were followed by large thickened lesions on the dorsal surface of the forearms and the external auditory canal He had severe constant pruritus Mild aches and pains of the bones and joints had occurred simultaneous to the cutaneous lesions but the bone pain had become quite severe during the preceding two weeks The liver was palpable 2 cms below the costal margin Roentgenograms of the bony skeleton disclosed punched out osteolytic lesions compatible with multiple myeloma involving the dorsal vertebrae ribs skull and iliac crest Laboratory studies were reported to show the urine positive for Bence Jones protein protein electrophoresis showed decreased gamma globulin although both beta and gamma glob

multiple myeloma (Hellwig 274, Waldenstrom, 703, Hill *et al*, 282 Barr *et al*, 30, Holmberg and Gronwall, 293, Packalen, 498, Flemberg and Lehman, 188b, Flemberg, 188a, Borvik, 574 and P F. Hansen and Faber, 258). The clinical and cutaneous manifestations of cryoglobulinemia are apparent as. (1) Raynaud's disease, (2) purpura with bleeding from the mucous membranes, (3) cutaneous ulceration and necrosis, (4) cold urticaria, and (5) cutis marmorata

Cryoglobulinemia is no longer considered to be a rare sign It has been suggested that cryoglobulins produce this varied clinical picture by causing stasis and sludging of blood with subsequent injury to the involved areas This theory has been substantiated by the postmorten findings of intravascular gelatinous material and by the presence of this process in retinal vessels It has also been suggested that certain simple tests for the detection of this condition should be done more frequently Barr *et al* (30) and Myerson and Stout (467) have described such tests One consists of cooling the blood serum to 4 deg C for a maximum of 72 hours The serum is then heated and prompt clearance of the precipitate indicates a positive reaction Cooling the serum in ice water will produce a gel which disappears when the serum is again warmed The length of time required for the gel to appear is dependent upon the amount of cryoglobulins present in the serum Another procedure consists of staining the peripheral blood with brilliant cresyl blue supravital stain and cooling the slide to 6 deg C Pinkish staining inclusions in the cytoplasm of the monocytes and polymorphonuclears indicate a positive reaction A quantitative determination of cryoblobulins, which has been most useful in determination of cold sensitivity, is obtained by dividing the serum into two portions and (1) the serum total protein albumin and globulin are determined, at room temperature, on the first portion, (2) the second portion is refrigerated overnight at 6 deg C and then placed in a high speed centrifuge for 30 minutes when the supernatent serum is separated from the precipitated proteins and the serum protein fractions are determined, and (3) the



Figure 67 Osteolytic lesions of the skull

of a cutaneous lesion revealed amyloidosis to be present in the cutis

B CRYOGLOBULINS The term cryoglobulinemia was first used by Lerner and Watson (382) to designate the presence in the blood of a cold precipitable serum globulin which dissolves upon warming When present in large quantities it is found as a solid white mass between the sedimented red blood cells and the supernatant plasma Although this finding has been observed occasionally in other diseases such as lupus erythematosus and periarteritis nodosa the majority of cases showing cryoglobulinemia have been demonstrated in

multiple myeloma (Hellwig 274, Waldenstrom, 703, Hill *et al*, 282 Barr *et al*, 30, Holmberg and Gronwall, 293, Packalen 498, Flemberg and Lehman, 188b, Flemberg 188a, Ronik, 574, and P F Hansen and Faber, 258) The clinical and cutaneous manifestations of cryoglobulinemia are apparent as (1) Raynaud's disease, (2) purpura with bleeding from the mucous membranes, (3) cutaneous ulceration and necrosis, (4) cold urticaria, and (5) cutis marmorata

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difference in the two globulin values represents the amount of cryoglobulins precipitated by the cold

Wintrobe and Buell (737b) described a patient who had multiple myeloma and Raynaud's disease There were symptoms of cold sensitivity, epistaxis, bleeding gums, mottling of the skin of the extremities, and thrombosis of the retinal vessels A somewhat similar case was reported by Lerner and Watson (382) Hutchinson and Howell (303) described a patient in whom cold precipitable globulins, demonstrated in association with Raynaud's disease, progressed to gangrene which required eight amputations Cugudda (132) described a patient with multiple myeloma and cryoglobulinemia who presented extensive gangrene of the right leg following roentgenotherapy Autopsy showed multiple arterial and venous thromboses Raynaud's disease, of a milder degree which was induced by exposure to cold, was present in six of the 10 patients with cryoglobulinemia who were reported by Barr *et al* (30)

Most cases of myeloma with cryoglobulinemia show a hemorrhagic tendency and purpuric cutaneous lesions which usually occur in areas exposed to cold On microscopic study, a precipitation of protein is found in the blood vessels of the skin (Snapper *et al* 642)

Rorvik's (574) patient, a 56 year old man, had hypostatic purpura in association with cryoglobulinemia In the months before his death, the hemorrhagic tendency became more marked and cutaneous ulcerations occurred Autopsy revealed diffuse infiltration of myeloma tissue in the bone mar-

tions of the legs for one year and later on the arms and thighs This bleeding was associated with exposure to cold, and she had a marked anemia The total globulin was not more than 3 1 per cent, but the cold agglutination fraction accounted for 1 3 per cent, or nearly one-half, of this total These investigators believed that the purpura could be as

cribed to a restriction of circulation due to intravascular precipitation of protein No other reasonable explanation of the hemorrhages could be found on examination of the blood In a later n bl

room temperature

Cutaneous ulcerations were previously reported in only three cases (Flemberg and Lehman 188b Flemberg 188a Rorvik, 574 and Steinhardt and Fisher 650) Flemberg and Lehman drew attention to the fact that the hemorrhages occur in areas having large cushions of fat under the skin In Rorvik's patient the ulcerations appeared in areas exposed to cold namely the nasal cavity and ears (although not on the hands or feet) or on areas abundant in subcutaneous fat. In the latter situation the ulcerations appear to have been preceded by necrotic processes with hemorrhages There was possibly a predilection for the small subcutaneous lipomas present in this case In sections from the edge of such an ulceration infiltration of myeloma tissue was found and therefore this may possibly have been the cause However myeloma tissue was also present in nonulcerated skin Rorvik believed it more reasonable to assume that the relatively poor circulation in fatty tissue together with the above mentioned properties of the blood caused these ulcerations in areas not particularly exposed to cold

The majority of these patients have a progressive anemia Waldenstrom (703) suggested that the high viscosity of the blood serum might give rise to functional disturbances n the bone marrow th

Pelzig (516)
globulinemia w ... ed as urticaria on exposure to cold Cold urticaria and purpura were reported to be allergic aspects of cryoglobulinemia by Steinhardt and Fisher (650) The patient described by Hutchinson and Howell (303) had a mottled or "blotchy" cyanosis of the hands and legs One Negro woman in Bluefarb's (56d) series presented



Figure 68 Ulceration of index and middle fingers associated with cryoglobulinemia (*A M A Arch Dermat*, 72 506, 1955)

a Raynaud-like syndrome with ulceration of the index and middle fingers Epstein and MacEachern (166) described a patient with plasmacytic leukemia who presented an ulceration, with a surrounding infiltrated red areola, involving the finger The histologic picture of this lesion established the diagnosis which was confirmed by examinations of the peripheral blood and sternal bone marrow They did not state whether this patient had cryoglobulinemia

C ELEVATED SERUM GLOBULINS It is of interest that two patients in Bluefarb's (56d) series had false-positive (Kahn) serologic reactions Snapper *et al* (642) stated that in myeloma patients who have recurrent pneumonia, there is a higher incidence of elevated serum globulin Allison and Dick (4) reported false-positive serologic reactions in patients having virus pneumonia It would appear that an elevation of serum globulins may lead to false-positive serologic reactions

Zinneman and Hall (755) reviewed the clinical histories of 64 patients who had multiple myeloma They found that there was a marked tendency toward recurrent bouts of bac-

terial pneumonia among these patients but their immediate response to antibiotic therapy was good Ten patients with multiple myeloma who did not have pneumonia were given polysaccharides of pneumonocci and brucellosis abortus and typhoid vaccine but their serum antibody response was poor They believed this evidence suggested that antibody production occurred in inverse ratio to the amount of abnormal serum globulins

Lawson *et al* (374) studied nine cases of multiple myeloma They found complete absence of antibodies or a marked deficiency of these substances to be a characteristic feature of multiple myeloma Although a definite abnormality was not initially apparent in a few cases repeated tests disclosed progressive decrease and ultimately complete or nearly complete disappearance of antibodies In five cases the serum protein was analyzed by filter paper electrophoresis In four cases there was a marked increase in gamma globulins while the fifth patient showed a tall peak of the "M component" but no gamma globulin Four of these patients had complete absence of antibodies including isoagglutinins while the fifth patient had almost complete absence of antibodies as well as no isoagglutinins The immunologic abnormality present in multiple myeloma has been considered to be the result of abnormal function of the malignant plasmacytes whereby deranged protein synthesis results in the production of abnormal proteins at the expense of normal proteins including antibody protein according to Lawson *et al*

Rostenberg Jr and Bluefarb (582) demonstrated that patients with myeloma have a depression of the immediate and delayed type of allergic reactivity

4 Cutaneous Manifestations Due to Cytopenias Anemia is one of the most important clinical findings in multiple myeloma It is almost invariably present and may be the only abnormal finding at the initial examination The anemia is usually of the normocytic type although iron deficiency anemia has also been noted Frequently there is an associated vitamin B deficiency Pallor is the outstanding clinical sign



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Figure 70 Agranulocytic membrane (*A M A Arch Dermat* 72 506 1955)

simulated acute leukemia and malignant granulocytopenia was considered in the differential diagnosis because of the history of sulfonamide therapy

About one third of these patients with multiple myeloma show an increased tendency to bleeding particularly from the nose (epistaxis) or gums The clotting factor is usually not defective although many patients have thrombocytopenia

Cutaneous purpura and petechiae may also be present The purpura usually results from infiltration of the blood vessel walls by amyloid resulting in damage to the vessel walls However this is not a complete explanation of the purpura, since amyloid is not always demonstrable in the blood vessel walls Snapper *et al* (642) called attention to the fact that these patients with a hemorrhagic tendency demonstrate a higher incidence of elevated serum globulins than the average patient who has no bleeding tendency Purpura was the presenting symptom in two patients described by Haines (251)

Three possible causes of purpura occurring with myeloma were advanced by Esser (171) (1) Damage to the bone marrow with secondary thrombocytopenia (2) damage to the liver with secondary derangement of the clotting mechanism and (3) vascular amyloidosis in the skin The reticuloendothelial system particularly in the liver is more frequently in-



Figure 69 Pallor and glossitis due to iron deficiency in a patient with multiple myeloma (*A M A Arch Dermat*, 72 506, 1955)

of this anemia Glossitis and koilonychia may be associated with iron-deficiency anemia One patient described by Snapper *et al* (642) had koilonychia

Meacham (492) called attention to the fact that macrocytic anemia may be present He stated that when macrocytic anemia, of unknown cause, occurs, a diagnosis of plasmacytic leukemia should be considered Three of Bluefarb's (56d) patients had macrocytosis which suggested pernicious anemia A smooth tongue was also noted in two of these patients

In the presence of leukopenia, numerous patients have an associated pyoderma When the bone marrow is replaced by plasmacytes, a granulocytopenia results and an agranulocytic membrane may be present on the gums This occurred in two of Bluefarb's (56d) patients

Soeborg-Ohlsen and Nielsen (644) described a 62 year old man who had two molar teeth extracted one month previously His temperature became markedly elevated and he was treated with "sulfonamide Redness of the throat, with cutaneous ulcerations and purpura occurred The condition

examinations revealed 6 2 gm /100 cc total protein and 1 6 gm /100 c
revealed
Patek
who had plasmacytic leukemia She presented various sized ecchymotic cutaneous lesions on the left hand and wrist thighs left groin and both pectoral regions The patient reported by Ghon and Roman (223) had anemia petechial hemorrhages and gangrene of the mouth Osgood and Hunter (496c) described a 49 year old man with plasmacytic leukemia who had bleeding from the gums and petechiae of the neck and upper chest

Case Report A 47 year old man entered the hospital in a stuporous condition He complained of vague pains in his back chronic cough and hemoptysis which had occurred one month previously On examination he appeared to be acutely ill He had Cheyne Stokes respiration and although he could be aroused he immediately fell into a stupor There was dullness in both upper lobes of the lungs the breath sounds were very harsh and there were inspiratory ronchi with prolonged expirations He had a "soft grade II systolic murmur of the heart and a "regular" tachycardia Laboratory studies of the feces disclosed a three plus benzadine reaction The clinical diagnosis at this time was pneumonia and chronic alcoholism Eight days later roentgenograms of his chest revealed enlargement of the heart and congestion of the lungs The spine showed demineralization and osteoarthritis The twelfth dorsal and first lumbar vertebrae were flattened and there was marked osteoporosis There were "punched out" lesions in the skull Biochemical studies performed two weeks later disclosed 24 mg /100 cc non protein nitrogen 5 2 mg /100 cc uric acid and 11 7 mg /100 cc calcium inorganic phosphorus The hemogram averaged 55 per cent hemoglobin 3 120 000 red blood cells and 9 940 white blood cells per cu mm with 65 per cent poly

volved as an extramedullary lesion Logically, this would lead to the speculation by Limarzi (391a) that hypothrombinemia may contribute to the cause of the bleeding in myeloma Another mechanism frequently mentioned is the uremia resulting from extensive renal impairment in myeloma The mechanism of bleeding, in this case, is due to toxic damage to the endothelium of the *smaller vessels, in* addition to further toxic depression of thrombocytopoiesis A patient described by James *et al* (316 case 2) had generalized ecchymoses



Figure 71 Purpura of the lower extremities

One of the patients reported by Bluefarb (56d case 8) was a 53 year old Negro who complained of loss of weight Examination revealed hepatosplenomegaly, and cutaneous petechiae and hemorrhagic lesions on the legs The hemogram was reported to show 52 per cent hemoglobin, 2 740,000 red blood cells and 13 400 white blood cells per cu mm, with 32 per cent polymorphonuclears 1 per cent band forms 29 per cent lymphocytes 3 per cent monocytes 2 per cent eosinophils, 33 per cent plasmacytes, and the nucleated erythrocytes 1 per *100 leukocytes The urinalysis revealed* four plus albumin the Bence Jones protein negative Biochemical

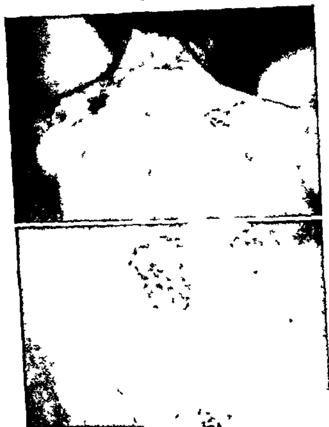


Figure 74 P rp ra and cut neous nodule on the back (case report)

Figure 75 Close-up of hemorrhag c nodule on back (case report)

minutes the clot retraction was complete the tourni quet test was negative and the prothrombin time was 12 minutes Electrophoresis revealed an increase in the gamma globulin, and decrease of the beta and alpha globulins and albumin These findings were considered to be characteristic of multiple myeloma The bio chemical examinations ranged from



Figures 72 and 73 Ecchymoses and purpura in a patient with multiple myeloma (case report)

morphonuclears, 16 5 per cent band forms, 14 5 per cent lymphocytes, and 4 per cent monocytes Examination of the aspirated sternal bone marrow revealed numerous plasmacytes, which were mostly mature forms, scattered in groups However, in some areas they occurred as "sheets" and in syncytium The erythropoiesis was normoblastic The diagnosis of multiple myeloma was established and urethane therapy was begun one month after he entered the hospital One month later marked cutaneous hemorrhages occurred on both sides of the trunk, together with raised, firm, indurated tender nodules which had a grey colored center The purpuric areas presented a reticulated pattern On examination 12 days later, the cutaneous lesions were very extensive They involved the trunk and neck, and the medial aspects of the thighs, which presented extensive areas of reticulated lesions Some of these lesions became necrotic and sloughed Further laboratory studies revealed a negative reaction for cryoglobulins and pyroglobulins The thrombocrit was 1 mm, the clotting time 15 minutes bleeding time 6



Figure 77 Close up showing deposition of calcium in artery (case report) Von Kossa staining

red blood cells per high power field Histologic study of a cutaneous nodule disclosed the characteristic deposition of calcium in the blood vessel walls This was interpreted as metastatic calcium deposition in the vascular walls

5 Toxic Cutaneous Lesions Many toxic cutaneous lesions such as alopecia are frequently associated with amyloidosis This subject was adequately reviewed by Goltz (234) However so-called "toxic cutaneous lesions not associated with amyloidosis may be present in multiple myeloma

Spiethoff (647) described a 58 year old man who had redness and pruritus of the face and hands and an indurated localized erythroderma A 39 year old man reported by Heidenstrom and Tottie (272) had polyarthritis and an "exanthem of follicular craters" on the extremities and buttocks A diagnosis of multiple myeloma was suggested by the finding of cryoglobulinemia in th patient described by Blades (50)



Figure 76 Histologic section of cutaneous nodule of Figure 75.

Albumin. 1 8 to 2.9 gm /100 cc
Globulin. 4.5 to 5.6 gm /100 cc
Total cholesterol 105 mg /100 cc
Icteric index 8 units
Non protein nitrogen 24 to 142 mg /100 cc
Creatinine 4 4 mg /100 cc
Phosphatase, alkaline 4 4 units/100 cc. (Bodansky)
Gamma globulin turbidity: 0 79 gm./100 cc.
Calcium inorganic phosphorus· 11 7 mg./100 cc.
Chloride: 93 meq./liter
Potassium. 3 5 meq./liter
Sodium. 133 meq./liter
Microscopic examination of the urine revealed 20 to 50

multiple myeloma are important and may be of aid in diagnosis, since they frequently occur early in the course of the disease Nonspecific ulcers of the leg have been observed

Witkov (740) reported a 58 year old man who had multiple myeloma associated with nonspecific, gangrenous, granulomatous cutaneous lesions involving the left lower extremity

6 *Cutaneous Manifestations Due to Myelomatous Involve-* [illegible]

[illegible] was occasionally present as a terminal manifestation of the disease

Lungs When pulmonary involvement (plasmacytoma of the lung) occurs, there is a possibility of hypertrophic osteopathia (clubbing of the nails) One patient in our series (56d) presented clubbing of the nails One of Plenck and Pretl's (528) patients and two of those described by Snapper et al (642) presented this symptom They called attention to the fact that the lunulae may disappear from the base of the nails even prior to the development of clubbing

Herpes Zoster A 60 year old man, described by Kobro (346 case 2), was known to have had multiple myeloma for two and one half years He had pain of the thorax and extremities, albuminuria, and Bence Jones proteinuria Herpes zoster then appeared in the fifth thoracic columnar area due to involvement of multiple myeloma A necrotic zoster on the right side of the chest was followed by intense postherpetic pain

A patient presented by Bluefarb et al (56j) was a 54 year old man in whom loss of weight and "anemia" had first developed four years previously Study of the sternal bone marrow at that time, disclosed multiple myeloma On examination, he had pain in the lower portion of the back and in the right lower posterior costal region He had frequent epistaxis and marked weakness A left pleural effusion had been present for three years but examinations for tubercle bacilli had been negative Cutaneous lesions had developed on the pos-

This patient also had xeroderma. Three patients in Bluefarb's (56d) series presented an associated cutaneous icthyosiform atrophy.

In this series (56d) the incidence of seborrheic dermatitis of the face appeared greater than that generally reported. *This dermatitis was of the oily "greasy" type and was most* prominent in the nasolabial folds. This characteristic seborrhea frequently led the hematologists to suspect the presence of multiple myeloma.

Canizares (96) cited two cases of multiple myeloma associated with cutaneous lesions. One patient presented several elevated purplish red plaques on the legs which were believed to be specific in origin. However, histologic examination disclosed a nonspecific inflammation. The second patient had multiple ulcerated lesions of the mouth which were resistant to therapy. Since the lesions in both cases did not respond to ordinary treatment but continued until death they were considered to be related to the multiple myeloma. Canizares believed that nonspecific cutaneous manifestations of



Figure 78 Herpes zoster associated with multiple myeloma

year Eight or nine months previously she had an acute episode of fever followed by markedly severe gangrenous herpes zoster involving the left lower extremity Several days later she presented generalized hemorrhagic bullous lesions generalized herpes zoster, with hemorrhagic bullae in the mouth, as well as on other areas of the body The zoster cleared after several months time leaving scars in the area on the left leg which had been involved with gangrenous lesions Several months later large bullae appeared in this scarred area but disappeared following the application of a "pressure bandage" Andrews believed this lesion might have been related to an epidemic of "shingles and varicella" occurring in the area at that time He also mentioned the tendency for these patients to have fungous infections His patient had moniliasis for many years even prior to the onset of multiple myeloma

B Treatment

1 Surgical Excision of Solitary Lesions

2 Roentgenotherapy to Involved Bones The lesions of multiple myeloma are usually not radiosensitive except in certain cases of solitary myeloma Sturgis (662b) recommended roentgenotherapy as the most satisfactory form of therapy, especially for the relief of pain associated with involvement of the bone

3 Stilbamidine Snapper *et al* (642) treated 15 patients having multiple myeloma with stilbamidine They reported that this therapy resulted in relief of pain but other manifestations of the disease such as hyperglobulinemia Bence Jones proteinuria and bone marrow abnormalities persisted

4 Urethane Rundles *et al* (589) treated 11 patients with urethane They noted reduction of the amount of abnormal protein and Bence Jones proteinuria However toxicity and relapse occurred 10 months later Harrington and Moloney (259) utilized urethane in 11 cases and found it to be effective in six patients There was relief of pain in nine cases and six patients gained in weight following treatment It was their impression that urethane therapy is more effective in chronic



Figure 79 Nonspecific ulcer of the leg

terior aspect of the left leg three weeks after admission to the hospital These lesions consisted of two erythematous areas which were painful, tender, ulcerated, and covered by crusts The skin was markedly pale and had a yellow tinge The liver was palpable 4 cms below the costal margin The hemogram revealed 38 per cent hemoglobin, 1,540,000 red blood cells and 3,200 white blood cells per cu mm, with 53 per cent polymorphonuclears, 25 per cent lymphocytes, 14 per cent monocytes, 5 per cent band forms, and 3 per cent eosinophils The hematocrit was 18 per cent, the sedimentation rate 77 mm per hour and rouleaux were present Biochemical examinations disclosed 13 2 gm /100 cc total protein, 2 1 gm /100 cc albumin, 11 1 gm /100 cc globulin and no Bence Jones protein was found Roentgenograms revealed 'punched-out" areas involving the pelvis and lumbar spine, compatible with the findings in multiple myeloma

Andrews (10c) described a woman who had purpura and aphthous ulcers associated with multiple myeloma for one

VII

NONSPECIFIC CUTANEOUS LESIONS ASSOCIATED WITH THE LEUKEMIAS

When nonspecific cutaneous lesions are associated with leukemia, they may precede the internal organ involvement or the specific cutaneous lesions by a period of weeks or years However they occasionally do not appear until late in the course of the disease The character or duration of these lesions is not constant in any one type of leukemia or in any one individual They may be protean and evanescent and may disappear and recur spontaneously without any obvious relation to the underlying disease process Specific cutaneous lesions may sometimes develop from these nonspecific lesions The head of the body appears to be more frequently involved with nonspecific than with specific cutaneous lesions

The most frequent nonspecific cutaneous lesions associated with chronic lymphocytic leukemia are prurigo like papules bullae purpura herpes zoster and exfoliative dermatitis while urticaria pigmentation herpes simplex eczematoid lesions pyoderma and trophic lesions occur less frequently Priapism is sometimes present

Nonspecific cutaneous lesions do not occur as frequently in granulocytic leukemia as in lymphocytic leukemia There have

... per cent, maculo papules in 3 3 per cent, vesicles in 2 2 per cent furunculosis

forms of this disease Saltzmann and Borgstrom (595) treated one patient with 1 5 gm of urethane, three times daily, for 20 days After the first 10 days of treatment the scalp nodules decreased in size and, after 20 days, the lesions disappeared, leaving depressions in the skull

5. Corticotropin (ACTH) and Cortisone. Cortisone and corticotropin appear to produce promising clinical remissions, as well as a reduction in abnormal globulins and plasmacytes, according to some investigators

6. Combined Therapy with Corticotropin, Cortisone and Urethane. Platzer (527) believed this combination to be the most promising form of therapy at the present time The simultaneous use of urethane and cortisone suggests a "synergistic action" in the few cases in which it has been used

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Nonspecific cutaneous lesions do not occur as frequently in granulocytic leukemia as in lymphocytic leukemia There have been occasional reports of prurigo like papules or hemorrhagic lesions such as purpura while herpes zoster and urticaria are rarely described E Epstein and MacEachern (166) reported that hemorrhagic lesions occurred in 30 per cent maculopapules in 33 per cent, vesicles in 22 per cent furunculosis

in 2 2 per cent and herpes zoster in 1 1 per cent of their patients who had all types of leukemia

Nonspecific lesions associated with monocytic leukemia usually involve the oral mucosa and consist of soreness bleeding from the gingivae, and swelling and necrosis of the mucous membranes which may extend to the tonsil or soft palate There may be purpuric lesions and widespread staphylococcic infections, including furuncles, carbuncles and abscesses, as well as exfoliative dermatitis The frequency of the different types of cutaneous lesions associated with monocytic leukemia were listed by Fairburn and Burgen (175)

Type of Cutaneous Lesion	*Number of Cases*	*Per Cent*
Purpuric	32	64
Maculo papular	16	32
Nodular	11	22
Suppurative	10	20
Exfoliative	6	12
Other Types	3	6

Although purpura was the most frequent cutaneous lesion in this series, maculo papular and nodular lesions were not rare

Cutaneous manifestations appear to be more frequent in lymphocytic than in other forms of leukemia, although the highest incidence of cutaneous involvement occurs in monocytic leukemia In analyzing 289 cases of lymphocytic leukemia from the literature, Beck (39a) found the following types of specific and nonspecific cutaneous lesions occurred

Type of Cutaneous Lesion	*Per Cent*
Tumors	50
Erythroderma	26
Herpes Zoster	26
Prurigo Like Papules	21
Bullae	10
Purpura	4
Varicella Like Eruptions	3
Urticaria	3

In this series, the ages of the patients ranged from 55 to 64 years, which was 10 years more than that for all the cases of

lymphocytic leukemia, and 69 per cent of these patients were men Lymphocytic leukemic tumors appeared in association with all nonspecific cutaneous manifestations but most frequently with herpes zoster when the tumors were localized in the scars of gangrenous zoster A relationship between the course of lymphocytic leukemia and its associated cutaneous manifestations was noted in herpes zoster, purpura and bullae combined with papules These manifestations usually occurred when the disease was fully developed The peripheral blood studies were normal only in the patients who had tumors and in a few who had papular eruptions There was splenomegaly in 40 per cent of the cases having purpura in contrast to splenomegaly in 25 per cent of the cases having other nonspecific cutaneous lesions

Inflammatory cutaneous infiltrates with no immature cells, are occasionally present in various types of leukemia and other lymphomatous diseases, according to Goldblum *et al* (230) They performed passive transfer tests and intracutaneous sensitivity tests on several patients in an attempt to determine the etiology of this condition The passive transfer tests were uniformly negative, indicating that circulating reagins are not responsible for leukemid reactions Sensitivity to serum and globulin was occasionally noted They concluded that fixed antibodies may be the "key to the problem"

1 Prurigo Like Papules (Prurigo Lymphatica)

The term "prurigo like papules" would seem to be preferable to "prurigo lymphatica" since morphologically, this same type of lesion occurs in Hodgkin's disease lymphosarcoma, tuberculosis dermatitis herpetiformis and occasionally, in malaria In some cases it is impossible to determine the cause of this nonspecific cutaneous lesion without peripheral blood studies sternal bone marrow examinations histologic examina[illegible]

[illegible] first described by Wagner (701) Clinically, the disease is characterized by pale, skin

colored edematous papules which are semiglobular or conical in shape and from 0 1 to 2 0 cm in size with a vesicle on the surface which is usually deep seated Because of intense pruritus the top of the vesicle becomes scratched off and is replaced by a crust These lesions have a marked tendency to recur after apparently complete regression following therapy As a result of scratching the skin between the papules becomes thickened hyperpigmented and edematous causing secondary pyoderma such as impetigo and furunculosis A concomitant swelling of the draining superficial lymph nodes

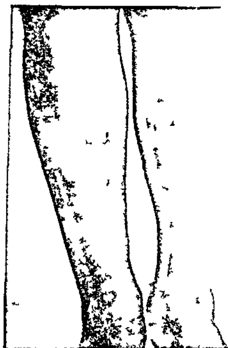


Figure 80 Prurigo like papules associated with lymphocytic leukemia

usually occurs Arndt (14b) also mentioned the morphologic resemblance of these lesions to those of prurigo of Hebra which is a disease affecting children that is rarely observed in the United States

Sakurane and Isura (594) described a 46 year old woman

who had a gradually increasing splenomegaly for about 18 months The hemogram revealed 2,700,000 red blood cells and 24 500 white blood cells per cu mm, with numerous immature granulocytes The spleen decreased in size and the white blood cells decreased to 7,200 per cu mm following roentgenotherapy Numerous brownish red, "pinhead" sized pruritic nodules then appeared on the extremities and extended to involve the trunk Roentgenotherapy was discontinued and the nodules disappeared after daily intravenous injections of Ringer's solution for 13 days However, the white blood cells increased to 18 500 per cu mm Histologic study of the cutaneous nodules revealed no leukemic change, although the changes which occur in prurigo Hebra were apparent

Prurigo-like papules may occur in chronic lymphocytic leukemia either in the leukemic or "aleukemic" phase Jordan and Schamschin (321) called attention to this type of lesion as the predominant cutaneous manifestation of "aluekemic" leukemia Among 10 cases of "aleukemic" leukemia, they found prurigo lymphatica to be of great importance since it was frequently the first indication of an 'aleukemic process and, therefore, helped to establish the diagnosis in doubtful cases Neither the clinical nor the histologic picture is sufficiently typical in the "aleukemic" phase to prove the leukemic nature of the disease Histologically, there are acanthosis spongiosis occasionally vesicle formation and inflammatory

[illegible]

scribed a patient who had cutaneous lesions associated with "aleukemic" myelosis

There [illegible]

go-like c [illegible]

In these [illegible]

studies r [illegible] diagnosis of leukemia

Riehl Jr s (562b) patient was a 65 year old man who had gradual loss of weight for the past eight months and labora-

tory studies revealed granulocytic leukemia For a period of three months, during his second course of roentgenotherapy, numerous exanthemata appeared on the face, scalp, neck upper extremities and part of the trunk, particularly on the breasts These lesions were 'hemp seed to small bean' size hard, light brownish red, scattered papules Severe pruritus then occurred and some of the scratched papules became crusted Some of the lesions became confluent and the face was slightly edematous There were a few ulcerated papules on the mucous membranes of the mouth and pharynx Histologic study disclosed a polymorphous round cell infiltrate consisting mainly of granulocytic cells which gave a positive oxydase reaction The hemogram revealed 56 per cent hemoglobin, 3 110,000 red blood cells and 18,800 white blood cells per cu mm, with 3 per cent polymorphonuclears, 2 per cent band cells, 2 per cent lymphocytes, 2 per cent monocytes, 2 per cent metamyelocytes, 1 per cent myelocytes, 1 per cent progranulocytes and 61 per cent myeloblasts Neumann (475) also mentioned a case of granulocytic leukemia in which the cutaneous lesions simulated those of dermatitis herpetiformis Cassavetis' (104) patient was known to have had "aleukemic" leukemia for seven years On examination there were bullous cutaneous lesions which simulated dermatitis herpetiformis that had been present for several months One of Hazen's (269 case 2) patients was a 57 year old man who had many groups of vesicular lesions on the face, scalp, arms, hands and trunk, most marked in the axillae The vesicles, from 3 to 4 cms in size, were, as a rule, on inflammatory bases but those on the face were on 1 cm papules The closely grouped vesicles which involved the scapular region were suggestive of herpes zoster and in one area they formed a superficial ulcer The skin of the face was generally thickened and edematous, with exaggerated furrows which resulted in a leonine facies This marked tendency toward vesiculo bullous lesions simulated the picture of a widespread dermatitis herpetiformis

The patient reported by Cleveland (116a, b) had Raynaud s disease and dermatitis herpetiformis two years before the de-





Figures 81 and 82 Bullous lesions in a patient with chronic lymphocytic leukemia

velopment of granulocytic leukemia Whitehouse (729a) reported a 45 year old woman with lymphocytic leukemia who first presented a cutaneous eruption on the forearms, then on

the face and legs, which finally became generalized and involved the palms and soles The lesions were hard, shotty, deep seated papules and vesicles, which showed a slight tendency to grouping They were quite red in color and inflammatory, and many were capped by a blood crust from being scratched The extreme pruritus, the chronicity of the eruption, and the grouping of the papules were all compatible with the diagnosis of dermatitis herpetiformis

A patient reported by Sharlit (627) had papular cutaneous lesions which were hemorrhagic and simulated Kaposi's sarcoma Gate and Cuilleret (213a case 2) described a 60 year old woman who had erythematous papular cutaneous lesions on the forearms, which resembled erythema nodosum, in addition to vesiculo bullous lesions on some of the erythematous infiltrations which simulated Duhring's disease Traub (688a) reported a 64 year old woman who had two types of leukemic cutaneous manifestations There was a true leukemic infiltration of the skin as well as a "toxic' eruption She had originally presented cutaneous lesions resembling erythema multiforme which were followed by an intensely pruritic vesiculo bullous eruption which simulated erythema multiforme or dermatitis herpetiformis Most of the cutaneous lesions and the lymphadenopathy disappeared following roentgenotherapy Histologic examination of a cutaneous lesion and an ulcerated lesion of the vulva disclosed leukemic infiltration A 48 year old woman described by Elliott (163), first had generalized pruritus which was followed by minute purpuric cutaneous lesions The papules gradually increased in size until they resembled the lesions present in urticaria pigmentosa The patient reported by Sibley (632) was a 41 year old man who had a fairly generalized macular cutaneous eruption for one month The lesions first appeared on the forehead but subsequently became very marked on the face, legs, arms and chest These lesions simulated those present in secondary syphilis, although there were no oral lesions and the blood serologic reaction (Wassermann) was negative A short time later many of these lesions became papular, particularly on

the forehead and scalp However, they disappeared after a few weeks but subsequently recurred on the forehead and gradually the entire face, scalp and almost the entire surface of the body became involved

Prurigo like papules are frequently described in leukemia and have a predilection for the extensor surfaces of the extremities A 53 year old woman, reported by Busman and Woodburne (88), had a diffuse follicular papular cutaneous eruption on the trunk, neck and extremities which was most pronounced on the back and abdomen The lesions were covered with a definite horny spine and were of a yellowish-brown color with a "peculiar sheen" which was "almost like that of lichen planus" The histologic structure was that "of a miliary, submiliary and conglomerate tuberculosis" Montgomery (459b) believed this case to be a tuberculoid reaction occurring as a result of true leukemic cutaneous infiltration thus simulating the reaction which occurs in "various forms of cutaneous syphilis, in which a tuberculous reaction" is frequently encountered but the treponema pallidum is found to be the etiologic agent Montgomery stated that he knew of only one case of lymphocytic leukemia in which a tuberculous cutaneous reaction occurred This patient, reported by Ramazzotti (545), had typical lymphocytic leukemia Cutaneous lesions which were both clinically and histologically papulonecrotic tuberculids developed and the tubercle bacillus was demonstrated This suggested, to Ramazzotti, a tuberculous etiology for both diseases

Skeer's (636b) patient was a 63 year old man who presented erythematous cutaneous papules scattered over the face, neck trunk, upper extremities and thighs The lesions were "pin head" sized on the trunk to "pea sized" or larger on the face and neck Some were conical and others round, while many were follicular and capped with a tiny vesicle, pustule or crust Others were flat, dark red or violaceous, particularly on the face, the majority had no areola, and appeared and disappeared spontaneously, leaving pigmentation There were areas of leukoplakia on the lower lip and on the inner aspect

of the cheeks near the corners of the mouth The blood serologic reaction (Wassermann) was four plus Histologic examination of the skin showed the epidermis to be corrugated and covered by stratified squamous epithelium with keratinizing *superficial layers and short, blunt, delicate rete pegs In some* places, hair follicles, sebaceous and sweat glands were present within the corium The broad papillae contained distended capillaries, lymphatics and an infiltration of small round cells There were monocytes and polymorphonuclears, particularly in the deeper portions of the cutis and about the appendages A few infiltrating cells appeared to be "young white blood cells" The cellular infiltration was also present about smaller blood vessels There was some edema of the interstitial tissue but no evidence of leukemic infiltration was present In com*menting on this case, Niles (480) stated that hemorrhagic le*sions would usually be found in a case having this long duration and he believed it unusual that this patient had no mucous membrane hemorrhage, epistaxis or bleeding gums It was his opinion that this case could be classed with "prurigo lymphatica," a condition occasionally present with granulocytic and more frequently, with lymphocytic leukemia He believed this eruption to be so called' because of its resemblance to the common prurigo which occurs in children and involves the outer surfaces of the extremities However, in leukemia, patients who have this form of prurigo are adults and the lesions tend to occur on the trunk as well as on the extremities

One of Cannon's (97a) patients was a three year old boy who had numerous toxic cutaneous lesions, as well as papular lesions He had a generalized pruritic eruption and numerous cutaneous papules and plaques which were most marked on the front *of the body The plaques were purpuric and the* papules were of a bright red color A few "pea" sized, red and hemorrhagic, eroded raised lesions were present on the mucous membranes of the cheeks, under the sides of the tongue, and on the right tonsil

Necrosis of the papular cutaneous lesions occurred in Hopkins' (295) patient who also had bullous lesions and leukemic nodules Ruiter and Van Bolhuis (588) described a 10 year old boy who had subacute granulocytic leukemia He presented a disseminated vesiculo papular cutaneous eruption which in some areas, particularly on the buttocks, became infiltrated and necrotic There were bluish red nodules on the neck and cheek which were elastic on palpation and the surface of some became "spongy" through loss of superficial tissue Histologic study of a cutaneous tumor disclosed granulocytic tissue, as well as "normoblasts"

J H Mitchell (455) presented a 49 year old man who had [illegible]

who had scattered cutaneous papules and numerous vesicles and small bullae. There were a number of nonulcerated tumors on the face which revealed on histologic examination, specific granulocytic leukemia cutis The papular and vesicular lesions however, showed only the usual inflammatory features The patient described by Steinbrinck and Stukowski (649) presented prurigo-like papules of a yellowish color which were polygonal, round and pruritic and, for the most part, transformed into resistant vesicles which later became crusted The localization on the extremities also was the same as that of prurigo Histologic study of the vessels revealed myelocytes and polymorphonuclears in the epidermis but there was no pronounced specific or nonspecific infiltration in the corium The cutaneous eruption was designated as a 'leukemid" Nonspecific papular cutaneous eruptions have also been described by Parade and Voegt (500) and Levin (384a)

Generalized papular cutaneous eruptions have been reported by Dubreuilh (155), Cheever (112), Nanta (470a), Ormsby (494c), and others Bouchut *et al* (68a) described a patient who presented papular cutaneous lesions, vesicles, bullae, and many hard nodules of cutaneous leukemic infiltra

tion Chargin's (110) patient was a 46 year old man whose cutaneous eruption involved the posterior aspect of the neck, the back (except the center), buttocks, legs, dorsal surfaces of the feet, abdomen and hands The lesions consisted mainly of closely placed "pinhead to pea" sized papules and nodular infiltrations present on a somewhat erythematous and infiltrated cutaneous surface There were numerous small, scattered pustules, resulting from secondary infection These prurigo like lesions were brownish or reddish brown in color, the recent lesions being red and the older ones varying shades of brown There was considerable evidence of scratching on all areas of the body and the severe pruritus was most marked on the lower extremities A 46 year old woman, reported by Small and Schmidt (637), had isolated, red cutaneous papules 5 to 6 mm in diameter, which had central pustules and an indurated base These lesions involved the right side of the neck, under the chin, the right axilla and the anterior aspects of both thighs Sannicandro's (596a) patient had a generalized polymorphous cutaneous eruption consisting of papules vesicles and nodules The most prominent and abundant lesions were "pea to filbert sized cutaneous nodules Histologic study revealed a dense infiltration of myeloblasts, eosinophils and thrombocytes present in the deeper portions of the cutis

Among Beeks (39a) 289 cases the prurigo like cutaneous lesions clinically resembled scabies, prurigo or lichen ruber and the prurigo like lesions which occurred with bullae in 26 per cent of the cases, somewhat simulated dermatitis herpetiformis

Beek believed it possible that a particular type of cutaneous lesion might be responsible for the different age incidence between patients having lymphocytic leukemia with cutaneous lesions and those not having cutaneous lesions He found this difference was not due to a special preference of one type of leukemic cutaneous manifestation in the older age group since all types of cutaneous manifestations in lymphocytic leukemia showed this preference His findings were as follows

Cutaneous Lesions, Per Cent	Age Years		
	Birth to 19	20-49	50 or More
Tumor	9	22	69
Prurigo-like Papules	—	31	69
Zoster	9	23	78
Bullae	—	22	78
Purpura	9	19	72
Erythroderma	3	29	68

These findings are in contradistinction to the decreasing functions of senile skin a similar occurrence to that present in cutaneous carcinoma

Beek also found that a relationship between the clinical course of lymphocytic leukemia and its cutaneous manifestations was apparent only in cases having herpes zoster, purpura and bullae combined with papules These manifestations usually occurred in fully developed lymphocytic leukemia Normal peripheral blood counts were present only in cases having tumors or, in a few instances, in those having papular lesions Splenomegaly was present in 40 per cent of the patients who had purpura and occurred only in ± 25 per cent of the cases showing other cutaneous manifestations such as tumors papules, zoster, erythroderma and bullae

2. Purpura

Hemorrhage is a frequent clinical manifestation in all types of leukemia These hemorrhages may occur in the skin and mucous membranes or in any organ of the body and may appear as isolated or multiple, diffusely distributed, purpuric lesions The hemorrhages may develop spontaneously or may result from trauma and may sometimes occur in association with a blood platelet deficiency However, the number of blood platelets may be normal or increased In some cases a tissue factor which causes fragility of the blood vessels may be present and in others an added factor, not manifest in the peripheral blood, causes direct damage to the smaller blood vessels or even rupture of these vessels There may also be a combination of all three of these factors Leukemic infiltrations are not of primary importance in the production of bleed-

ing Abnormal bleeding usually occurs as petechiae particularly in acute leukemia Purpura in the form of petechiae and ecchymoses are more frequent extensive and of longer duration in chronic lymphocytic leukemia than in chronic granulocytic leukemia

According to Minot and Buckman (454a) the hemorrhagic manifestations of thrombopenia are nearly always present for a few weeks before death but in some cases they may appear only a few days before death However varying degrees of petechiae and ecchymoses frequently appear many months or as long as two years preceding death A history of "black and blue marks" and a slight bruising tendency for many years is often described Patients who had purpura for many years preceding the development of leukemia were reported by Minot and Isaacs (454c) Among 80 patients who had leukemia for an average of 3 45 years they found at least 10 per cent had purpuric lesions one year before death However in this series purpura did not occur in many patients having less than 60 000 blood platelets at which level purpura is not usually expected to occur although purpura did appear as the terminal stage of the disease appeared The actual decrease of blood platelets does not seem to indicate the degree of hemorrhage in different patients or even in the same patient at different periods in the course of the disease This is one of the striking and unexplained relationships between the number of blood platelets and spontaneous bleeding

The hemorrhagic diathesis is particularly distressing in acute leukemia and in the acute exacerbations of chronic leukemia It has been suggested that an important factor in bleeding associated with leukemia is dependent on damage to the integrity of the blood vessel walls

Purpuric manifestations or other bleeding phenomena occurring in acute leukemia may be satisfactorily explained on the basis of the numbers of decreased blood platelets according to Forkner (192b) In chronic leukemia however the bleeding tendency may occur without apparent abnormal

ity in the elements concerned with blood coagulation. Such bleeding is often associated with microscopic or macroscopic perivascular infiltration of leukemic cells and, Forkner stated, may be at least partly explained on the basis of invasion or injury to the blood vessel walls. There is frequently no adequate explanation for the bleeding in leukemia, a problem which has been inadequately studied up to this time.

Lymphocytic Leukemia. Hemorrhagic tendency is frequently a prominent and sometimes a very early symptom of lymphocytic leukemia. Warren (708) summarized 113 cases in which the diagnosis of lymphocytic leukemia was confirmed at autopsy. He found that 30 to 40 per cent of these patients had prolonged epistaxis following tonsillectomy, dental extraction or minor surgery. Epistaxis, bleeding gums, intestinal hemorrhage, petechiae or larger hemorrhages in the skin or mucous membranes, may occur. The purpuric lesions may become necrotic or bullous, as described by Shattuck (628). A 60 year old woman who had ecchymoses and thrombopenia associated with chronic lymphocytic leukemia was described by Sabrazes (591). Both lower extremities were covered with ecchymoses and petechiae. Ecchymoses resulted from even moderate scratching. This tendency to the production of ecchymoses and petechiae as a result of slight trauma was believed to be due to the prolonged bleeding time.

Naish and Tingle (469) described a 16 year old boy who had injured the middle finger of his right hand. The wound became infected and was incised. Three weeks later enlarged [illegible] and chin. The eyes were "half closed" due to the edema and there were large subconjunctival hemorrhages. There were numerous purplish [illegible] papules. The hard and soft palates, including the alveolar area, were swollen and infiltrated with ecchymotic areas. There was little change in the cutaneous

discoloration during the following month However, the color then became much deeper and several months later the skin of the face was "nearly black" The ecchymoses on the chest disappeared shortly after admission to the hospital and did not recur, but a mottled purplish discoloration appeared on the tibiae The discoloration of the skin gradually became lighter and at the time of death, 11 months after injury, it was less marked than at the time he entered the hospital

A 58 year old man, reported by Wintrobe and Mitchell (737c case 14), had specific cutaneous nodules and purpuric areas on the back associated with lymphocytic leukemia The patient described by Garvey and Lawrence (212) had purpura on the forearm and on the tonsils It was thought that purpura on the tonsils is always indicative of leukemia unless proved otherwise Gonin's (235 case 2) patient, a 58 year old man, had purpuric lesions on the shoulders, arms and mucous membranes of the mouth

Hitschmann and Lehndorff (287b) reported a 34 year old woman who had maculo papular cutaneous lesions on the abdomen and chest which first resembled lesions of syphilis but later became hemorrhagic She also had lymphadenopathy and splenomegaly The patient described by Best (45a) had "copper' colored, "split pea" sized, diffuse cutaneous macules which simulated a "fading syphilitic roseola" Whittaker (730) reported a 64 year old woman who had leukemia and "moderate' anemia for 10 months and purpuric lesions for six months Wawersig's (711) patient was a 68 year old man who had generalized purpura Cutaneous hemorrhages have also been described by Jakac (315) and Orhel (493)

Granulocytic Leukemia Purpura in the form of petechiae and ecchymoses, is the most frequent cutaneous manifestation of chronic granulocytic leukemia, despite the fact that thrombocytopenia rarely occurs in this type of leukemia

The tendency to a hemorrhagic diathesis is less frequent in chronic granulocytic leukemia than in chronic lymphocytic leukemia because the thrombocytes are usually increased in granulocytic leukemia However during acute exacerbations



Figure 83 Purpura associated with granulocytic leukemia (*A M A Arch Dermat* 73 189 1956)



Figure 84 Purpura in linear arrangement (vibices) associated with granulocytic leukemia (*A M A Arch Dermat* 73 189 1956)

or in the terminal stage of the disease chronic bleeding is frequently a characteristic feature of chronic granulocytic leukemia The bleeding usually occurs from the buccal or nasal mucosa or as cutaneous petechiae

Rolleston (572a) believed that cutaneous hemorrhages may

occur in the terminal stages of the disease and are probably due to an acute exacerbation of chronic granulocytic leukemia Nekam, Jr (472b) found cutaneous hemorrhages to be the most frequent sign of granulocytic leukemia He believed they were due to an alteration of the vascular wall According to Sturgis (662a), purpura is the only frequent cutaneous manifestation which occurs in chronic granulocytic leukemia The cutaneous hemorrhages may consist of petechiae, occasionally ecchymoses, occurring with or without other cutaneous manifestations

Pearce (512) reported a "young" Negro whose primary symptom of chronic granulocytic leukemia was large subcutaneous hemorrhages which developed spontaneously or following slight injury Among 47 cases studied by Vogel (699), two patients had multiple evanescent tumors which apparently resulted from hemorrhages deep in the subcutaneous tissue

One patient reported by Jaffe (314h) had petechial cutaneous hemorrhages associated with chronic granulocytic leukemia, while another had hemorrhages involving the skin and mucosa of the lips, with granulocytic leukemia He also described a 43 year old man who, four weeks previously, had epistaxis which continued for four hours, recurred the following day, and required "packing" Subsequently spontaneous cutaneous hemorrhages occurred on the arms and legs as well as bleeding from the gums, during the rapid course of the disease A 14 year old girl, reported by Rolleston (572a), had chronic granulocytic leukemia She had transient subcutaneous hemorrhages on the lower extremities One of these lesions had followed trauma The predominant clinical symptoms in Tischendorf's (685) patient were the purpuric manifestations A 55 year old man who had polycythemia eventuating in granulocytic leukemia was reported by Zimmermann (754) He first had pain in the right shoulder and several days later, hemorrhages appeared over the entire right arm and right side of the chest The bluish cutaneous hemorrhages spread over the entire surface of the trunk and extremities following roentgenotherapy

Cannon (97a) described a 45 year old woman whose initial complaints were "black and blue spots" on the skin and bleeding gums She had previously had lupus erythematosus There were 15 to 18 "dime sized" deeply pigmented, macular cutaneous lesions which did not fade on pressure and were swollen dark red in color and showed evidence of hemorrhage A 50 year old woman presented by Peck (514), had shortness of breath weakness and generalized pruritus for eight years An unusual pigmentation which began on the legs and progressed to involve the pelvic region, had occurred during this same period of time There were numerous varied sized brownish red macules, which did not disappear with pressure and appeared to be hemorrhagic, involving only the legs, but the arms and abdomen showed evidence of scratching The first symptoms of subacute "aleukemic" granulocytic leukemia evidenced by the 50 year old woman reported by Nissen (481) were fever, ulcerations of the mouth and lips, and cutaneous hemorrhages

Erf's (168a) patient was a 44 year old woman who had bleeding gums "hard," tender breasts and "purple spots" on the skin She had large hemorrhages in each retina, bilateral subconjunctival hemorrhage and generalized lymphadenopathy Reyn (556) described a 49 year old man who had gangrenous cutaneous ulcerations associated with "aleukemic" granulocytic leukemia He first had cutaneous *hemorrhages*, vesicles and pustules which later became necrotic ulcerations He had a leukopenia of 2,200 cells per cu mm The infant reported by H M Keith (335a) presented small, dark, scattered cutaneous macules at three weeks of age They remained for several days and disappeared spontaneously A macular cutaneous eruption, which first developed as small blisters and later became hemorrhagic and surrounded by a red areola appeared on the scalp and arms at seven months of age The *blisters tended* to ulcerate and become crusted This eruption, present nearly constantly until the child was 15 months old *suddenly* increased in severity and numerous dark hemorrhagic lesions appeared

A 72 year old woman who had a purpuric eruption on the legs and upper chest for three months was reported by Polson (535). She also had painful swelling of the joints of the hands, loss of weight, poor appetite and constipation There were petechial hemorrhages on the arms, back, hips and left shoulder, some of which were ecchymotic She also had hepatosplenomegaly One year later she presented a 7 0 by 5 75 cm ulcerated lesion on the inner aspect of the middle third of the left leg, as well as a purpuric eruption on the extremities and anterior wall of the chest Histologic examination of this lesion revealed massive infiltration of the ulcer and adjacent corium by mature and immature granulocytes Polson believed that the ulcer resulted from the granulocytic deposit causing devitilization of the skin

Monocytic Leukemia. Petechiae usually occur in monocytic leukemia and hemorrhages of the mucous membranes and skin tend to occur when the blood platelets are reduced in number However, patients having purpura with a normal blood platelet count have been reported The purpuric lesions are usually generalized Petechiae may develop into papules or vesicular bullous lesions However, when several types of cutaneous lesions coexist, the purpura precedes the terminal stage of the disease Histologic study of these lesions, according to Fairburn and Burgen (175), revealed monocytes in the capillary adventitia and infiltrating the periphery of the extravasation, in some cases, but the monocytes were usually prominent within the vessel Herbut and Miller (277) noted cutaneous lesions in six of their eight patients There were innumerable pinpoint to 2 mm sized scattered petechiae, having no particular site of predilection The lesions were flat and not indurated although in one patient (case 7) the surrounding subjacent tissue contained definite firm grey, 1 to 2 mm foci Two patients had intracutaneous and subcutaneous hemorrhages up to 14 cms in diameter Centrally, these lesions were slightly elevated but peripherally they gradually merged into the normal adjacent tissue They (277 case 4) described a 40 year old man who had symptoms

of peptic ulcer" for several years He had soreness and bleeding of the mouth as well as "black and blue spots" on the skin for one week preceding entrance to the hospital, at which time he was in coma Hemogram disclosed 42 000 white blood cells per cu mm, with 20 per cent monocytes and 68 per cent monoblasts He died eight days after the acute symptoms appeared Another patient (case 7) also had purpuric cutaneous lesions

The 56 year old man reported by C B Wright and Norris (744) first presented purpuric macules over the body He died two months after onset of the disease Boles *et al* (62) described a 13 year old girl who had bleeding from the mucous membranes of the lips and petechiae on the eyelids and right breast She had moderate generalized lymphadenopathy and the spleen and liver were palpable L A Mitchell's (456) patient, a 63 year old man, first had general weakness, persistent abdominal distention and discomfort, and slightly palpable, *reddish cutaneous lesions on the legs These lesions* were found to be due to intracutaneous infiltration There were a few "pea" sized, firm, discrete subcutaneous nodules on the lower part of the abdomen These lesions later increased to "about 200" in number and involved the trunk, arms and scalp The majority of the lesions were freely movable in [illegible]

[illegible] jections of sodium cacodylate and the nodules numbered only 25 However, the nodules again increased to "about 100" in number and the testicles enlarged to twice normal size Both the nodules and the swelling of the testicles decreased following irradiation therapy Hepatosplenomegaly, oozing of blood from the gums, small subcutaneous hemorrhages, and small hemorrhages from the colon occurred 10 days before death He died eight months after onset of his illness Coste *et al* (126) described a 54 year old man who had chronic purpura with yellow colored cutaneous pigmentation which became generalized, as well as extensive isolated "placards" which appeared and disappeared spontaneously

These cutaneous manifestations appeared during a period of 15 months There were widespread cutaneous lesions yellowish brown and brownish red in color which were dry non scaling and atrophic The lesions were initially accompanied by paresthesia pruritus and a feeling of "warmth" Ecchymotic hemorrhages due to increased capillary fragility also occurred

Among the cases reported by Lynch (409a case 1) one was a 67 year old man who presented a lesion on the penis following a chemical burn The lesion became ulcerated and painful enlargement of the shaft and glans was associated with weakness chills and fever Despite therapy the necrotic ulceration progressed and numerous petechiae some 2 cms in diameter appeared over the entire body while subconjunctival hemorrhages also occurred The course of the illness was febrile and he died five weeks after the initial symptoms had appeared Another patient (409a case 3) was a 66 year old man who had numerous petechiae in the scapular and clavicular regions and ecchymoses on the extremities The purpuric tendency disappeared following four transfusions of whole blood Another patient (409a case 4) had scattered petechiae followed by subcutaneous hemorrhages on the trunk and extremities Histologic study of a petechial area showed no change in the capillaries there was only extravasation of red blood cells There were no specific changes in the perivascular tissues

Case Report One year previously this 33 year old woman had a premature (7 month) infant who died of pulmonary complications 24 hours after birth She had pain in the back and epigastrium for some time preceding delivery and had vomited for several days before delivery She had severe epigastric pain on the first post partum day at which time the hemogram revealed 3 150 000 red blood cells and 53 400 white blood cells per cu mm The following day there were 2 700 000 red blood cells and 123 000 white blood cells per cu mm Transfusions of whole blood were administered

during the next two days and she was given Pantapon®, penicillin, streptomycin, testosterone and stilbesterol On examination, one year later, she appeared apprehensive and was perspiring profusely. Her pulse rate was 116 and the respirations 32 per minute, and temperature 101 deg F She had hemorrhagic lesions on the right cheek, lower lip and posterior pharynx and the gums were hyperplastic and bleeding There was crusted blood in the nostrils, the conjunctivae were pale and the sclerae non icteric There was a large chain of lymph nodes involving the anterior and posterior cervical and postauricular regions Although the lymph nodes were not tender, the breasts were painfully engorged The spleen was tender to palpation and enlarged 4 to 6 cms below the costal margin, while the liver was slightly tender and enlarged 10 to 12 cms below the costal margin There was inguinal lymphadenopathy. She was given transfusions of whole blood and radioactive phosphorus (3 millicuries) Ten days later many ecchymotic areas had appeared on the skin and there were numerous small pustules on the scalp The following day she became jaundiced and there was partial ptosis of the left eyelid The next day she became disoriented and had hallucinations Two days later her condition seemed improved and the hepatosplenomegaly had decreased However, the following day she became comatose, marked dyspnea occurred, the cutaneous infiltrations became more marked and hemorrhagic, and a deep, extensive infiltrative ecchymoses involved the entire abdominal wall Hemogram revealed 2 360,000 red blood cells and 118,000 white blood cells per cu mm, with a majority of promonocytes and a few monoblasts Three days later there were 3,810,000 red blood cells and 81,000 white blood cells per cu mm, with 75 per cent monocytes She died 15 days after admission to the hospital.

Among the cases of monocytic and histiocytic leukemia

reported by Belding *et al* (41) epistaxis bleeding from the gums and purpura occurred more frequently in the monocytic (Naegeli) type than in the histiocytic (Schilling) type The fact that these symptoms were not directly related to thrombocytopenia is evidenced by the fact that in all cases of histiocytic leukemia there was a definite thrombocytopenia but only two patients had significant hemorrhagic manifestations Furthermore among the four patients with monocytic leukemia who had no diminution of the blood platelets two exhibited very definite hemorrhagic tendencies

A 59 year old woman reported by Costello *et al* (127b case 3) had weakness and loss of weight for six months following influenza Petechiae and "blotchy" superficial ecchymoses occurred two months later and large hemorrhagic bullae appeared on several occasions On examination the skin was of a lemon yellow color and xerotic, with numerous petechiae ecchymoses and stellate and linear vibices Small axillary lymph nodes were palpable The hemogram showed 5 4 gm hemoglobin per 100 cc 1 900 000 red blood cells per cu mm with 6 per cent reticulocytes and there were 13 400 white blood cells per cu mm with 79 per cent polymorphonuclears 2 per cent band forms 11 per cent lymphocytes 6 per cent myelocytes and 1 per cent eosinophils Study of the sternal bone marrow disclosed a hyperplastic marrow with an increase in granulocytes and rubriblasts The myelocytes and myeloblasts were increased in number Two months later she had numerous ecchymoses and vibices while the superficial veins exhibited a glistening violaceous coloring The peripheral blood count now showed 3 6 gm hemoglobin per 100 cc 1 300 000 red blood cells and 52 000 white blood cells per cu mm with 47 per cent neutrophils 2 per cent metamyelocytes 5 per cent basophils 1 per cent eosinophilic myelocytes 10 per cent neutrophilic myelocytes 3 per cent micromyelocytes 4 per cent progranulocytes and 28 per cent myeloblasts There was no beneficial response to therapy and she died two months later

Case Report A 48 year old man with chronic lym

phocytic leukemia had epistaxis, which continued for 60 hours, followed by bleeding from the gums and small purple colored lesions scattered over the trunk, most marked on the lower extremities He had several areas of submucous membrane hemorrhage with gross bleeding along the alveolar ridge He also had hepatomegaly and pain in the muscles of the legs There were petechiae of the conjunctivae and in the mucous membranes of the mouth and pharynx The hemogram revealed 65 per cent hemoglobin 3 020 000 red blood cells and 11,700 white blood cells per cu mm, with 23 per cent polymorphonuclears 77 per cent lymphocytes and there were 45 300 blood platelets Histologic study of tissue from the nose revealed necrotic changes of the cartilage with extensive infiltration of inflammatory cells around the edges The cells were mainly polymorphonuclears He died 11 days after examination and autopsy revealed minute, hemorrhagic petechiae of the skin and mucous membranes and superficial lymphadenopathy There were numerous [illegible]

diagnoses were lymphocytic leukemia, and hemorrhages in the skin, mucous membranes and gastrointestinal tract. Histologic studies revealed almost the entire spleen to be replaced by lymphocytic cells The lymphoid follicles were not evident and the capsule was invaded All the sinusoids of the liver were filled with lymphocytes and there were nests of lymphocytes in the portal areas The muscle fibers of the heart were pale, the cross markings indistinct and there was some fragmentation There were focal aggregations of lymphocytic cells throughout the heart

Case Report A 41 year old man, who was acutely ill, presented a "flushed" face, although there was marked pallor of the skin and the tongue was "pale"

with slight purpura on the edges He had splenomegaly and the hemogram revealed 1,800,000 red blood cells and 1,400 white blood cells per cu mm There were 55 800 blood platelets The clinical diagnoses were chronic 'aleukemic" granulocytic leukemia, marked secondary anemia and cardiac disease Two months later the splenomegaly had increased and he had marked generalized purpura There were now 1,700 000 red blood cells and 89,500 white blood cells per cu mm in the peripheral blood He died the following day and, at autopsy, there were hemorrhagic petechiae of the neck chest, abdomen and sclerae, while the buccal mucous membranes were markedly 'pale His tologic examination of the skin disclosed a small nest' of granulocytes and young polymorphonuclears, as well as some hemorrhage The anatomical diagnoses were granulocytic leukemia, with infiltration of the skin, spleen and liver, secondary anemia and cutaneous hemorrhagic petechiae

3. Herpes Zoster

The occurrence of herpes zoster in association with leukemia appears to represent a definite relationship rather than a mere coincidence

From a study of the reported cases, herpes zoster appears to be frequently associated with lymphocytic leukemia rarely with granulocytic leukemia and has been reported only once in association with monocytic leukemia (561)

Herpes zoster was defined by Carter and Dunlop (102) as an acute posterior poliomyelitis due to the virus of chicken pox However other investigators believe that herpes zoster results from injury to the posterior ganglions either from an acute specific virus or by another form of trauma This virus is frequently present in normal ganglia but is activated in some way, by other disease processes to produce herpes zoster The most common trigger factors according to Baird (22), are (1) drugs (arsenic, lead bismuth mercury, iodides, gold,



Figure 85 Herpes zoster associated with lymphocytic leukemia

morphine, carbon dioxide and carbon monoxide), (2) blood dyscrasias (particularly leukemia and Hodgkin's disease), (3) trauma, (4) infectious diseases (influenza, encephalitis, erysipelas, tuberculosis and syphilis, particularly early cardiovascular syphilis, paresis and tabes), (5) vaccination, and (6) malignant tumors (in which case the lesions cause pressure on the ganglion or the toxic effects result in herpes zoster) Leukemic infiltration may be localized in the spinal ganglion, thus producing zoster, according to Kumer (360)

Herpes zoster is one of the most frequent toxic cutaneous lesions associated with leukemia but this phase has not received notable attention in the American literature Herpes zoster occurs more frequently in patients having leukemia or lymphomatous diseases than in the general population, ac-[illegible]

re

lished cases described in this volume), 81 had lymphocytic leukemia (the "aleukemic" lymphocytic leukemia cases are also included since, in our opinion these patients had lymphocytic leukemia), 17 had granulocytic leukemia, one had monocytic leukemia and in six cases the type of leukemia was not mentioned

Beek (39a) reviewed 289 cases of lymphocytic leukemia and found that 48 per

associated with tumor

and 4 per cent pru

occurred in 58 per cent of the cases

The only report of monocytic leukemia associated with herpes zoster was that by Bluefarb (56a) In this case the monocytic leukemic cells were demonstrated in the spinal ganglion and in the intercostal nerves, which was the site of the herpes zoster This patient, a 54 year old man first had weakness, shortness of breath and a "productive" cough four years previously Sore throat and several attacks of epistaxis had occurred during the two months prior to examination The skin was of a lemon yellow color, resembling that of

pernicious anemia There was a hemorrhagic herpes zoster on the left lateral side of the chest and back which followed a course parallel to several of the ribs The spleen was palpable two finger breadths below the costal margin and the edge of the liver was palpable The hemogram revealed 26 per cent hemoglobin, 1,360,000 red blood cells and 113 700 white blood cells per cu mm, with 51 2 per cent monocytes, 5 6 per cent monoblasts, 3 2 per cent lymphoblasts 13 6 per cent myeloblasts, 8 8 per cent myelocytes, 5 6 per cent lymphocytes and 12 per cent segmented cells There were 8 normoblasts per 100 white blood cells and numerous nucleated red blood cells The hematologic diagnosis was monocytic leukemia The blood serologic reaction (Kahn) was positive The clinical course of the disease was fulminating A short time later he had numerous petechiae on the soft palate, lips, mouth trunk and abdomen Discrete, soft, 0 5 to 2 5 cm palpable lymph nodes appeared in the cervical inguinal, axillary and epitrochlear regions He died one week after admission to the hospital At autopsy there were two petechial hemorrhagic areas on the lower left eyelid and a 5 mm, centrally ulcerated, firm nodule was present near the inner canthus of the left eye The skin was 'pale' and greyish white in color and the mucosa of the lips and mouth were purplish grey There were numerous 0 5 to 1 mm, bright purplish red cutaneous lesions over the chest and upper part of the abdomen Numerous dry, superficially crusted, slightly elevated, deep purple-red papules up to 3 mm in diameter extended from the midline of the back anteriorly and downward in the regions of the sixth and seventh ribs The liver weighed 2,515 gm, its consistency was diminished, the capsule thin and the surface smooth On sectioning it appeared pale yellow grey in color and the lobular centers were of a lighter yellow color The thoracic aspect of the spinal cord (left seventh spinal ganglion) showed dark brown pigment in many of the ganglion cells A few of these cells were shrunken while in others the Nissl substance was poorly defined and the cytoplasm appeared finely granular There was a distinct prolifera

tion of the capsule cells In the fat tissue about the ganglion there were focal accumulations of monocytic cells Examination of the left sixth and seventh intercostal nerves revealed numerous infiltrations of monocytic cells along the nerves These cells filled the small blood vessels within the nerves and there were also small interstitial perivascular accumulations of monocytic cells Study of the lymph nodes revealed dense accumulations of monocytic cells and myelocytes, filling the lumen of the sinuses and infiltrating the trabeculae, encroaching on the secondary nodules of the cortex and reducing them to small and isolated islands of lymphocytes The ratio between the monocytic and granulocytic cells was about 3 to 1 Among the latter, well developed myelocytes were the most numerous Myeloblasts matured to metamyelocytes and leu



Figure 86 Focal accumulations of monocytes in the spinal ganglion (*Arch Dermat & Syph* 57 319, 1948)

pernicious anemia There was a hemorrhagic herpes zoster on the left lateral side of the chest and back which followed a course parallel to several of the ribs The spleen was palpable two finger-breadths below the costal margin and the edge of the liver was palpable The hemogram revealed 26 per cent hemoglobin, 1,360,000 red blood cells and 113,700 white blood cells per cu mm, with 51 2 per cent monocytes, 5 6 per cent monoblasts, 3 2 per cent lymphoblasts, 13 6 per cent myeloblasts, 8 8 per cent myelocytes, 5 6 per cent lymphocytes and 12 per cent segmented cells There were 8 normoblasts per 100 white blood cells and numerous nucleated red blood cells The hematologic diagnosis was monocytic leukemia The blood serologic reaction (Kahn) was positive The clinical course of the disease was fulminating A short time later he had numerous petechiae on the soft palate, lips, mouth, trunk and abdomen Discrete, soft, 0 5 to 2 5 cm palpable lymph nodes appeared in the cervical, inguinal, axillary and epitrochlear regions He died one week after admission to the hospital At autopsy there were two petechial hemorrhagic areas on the lower left eyelid and a 5 mm, centrally ulcerated, firm nodule was present near the inner canthus of the left eye The skin was "pale" and greyish white in color and the mucosa of the lips and mouth were purplish grey There were numerous 0 5 to 1 mm, bright purplish red cutaneous lesions over the chest and upper part of the abdomen Numerous dry, superficially crusted, slightly elevated, deep purple-red papules, up to 3 mm in diameter, extended from the midline of the back anteriorly and downward, in the regions of the sixth and seventh ribs The liver weighed 2,515 gm, its consistency was diminished, the capsule thin and the surface smooth On sectioning it appeared pale yellow-grey in color and the lobular centers were of a lighter yellow color The thoracic aspect of the spinal cord (left seventh spinal ganglion) showed dark brown pigment in many of the ganglion cells A few of these cells were shrunken, while in others the Nissl substance was poorly defined and the cytoplasm appeared finely granular There was a distinct prolifera-



Figure 88 Monocytes in a lymph node Myeloblasts and plasmacytes are also quite numerous (*Arch Dermat & Syph*, 57 319, 1948)

	Per Cent
Neutrophilic myelocytes	6 1
Neutrophilic leukocytes	0 9
Eosinophilic myelocytes	0 1
Mast cells	0 1
Erythrogonias	0 3
Erythroblasts	3 7
Normoblasts	13 9
Lymphocytes	0.5
Plasma cells	1 8
Megakaryoblasts	0 6
Megakaryocytes	0 5'

The monocytic cells tended to form groups in which there were few other marrow cells However, they also appeared scattered between the granulocytic elements The megakaryocytes often showed regressive changes The sinusoids were relatively narrow. The spleen weighed 390 gm and the consistency was diminished The capsule was slightly thickened and the surface smooth On sectioning, it was light purple-grey in color, soft and medullary The follicles were prominent The pulp was extremely cellular and closely resembled that of the bone marrow. The same types of cells were observed in approximately the same numerical relation Plasmacytes were more numerous than in the bone marrow and

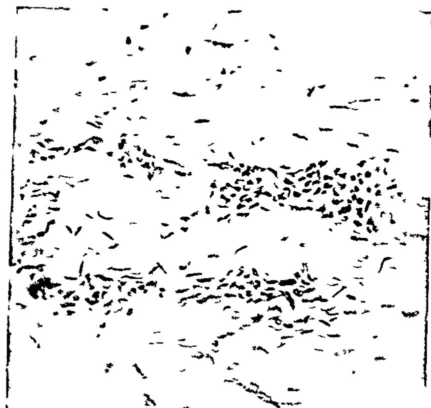


Figure 87 Monocytes in the spinal nerve The small blood vessels within the nerves are filled with these cells and there are also small, interstitial, perivascular accumulations of monocytes (*Arch Dermat & Syph*, 57 319, 1948)

kocytes in an orderly fashion Myeloblasts, with a characteristic nuclei, were fairly numerous, as were the plasmacytes, but the megakaryocytes were few in number and no nucleated red blood cells were found There was no iron pigment but some of the swollen reticulum cells contained erythrocytes or monocytic cells and myeloblasts Study of the bone marrow from the femur showed the cellularity to be 93 per cent This examination was reported to show

	Per Cent
'Monocytoid cells	71 2
Myeloblasts	0 3

leukemia and the oldest was an 81 year old woman who had lymphocytic leukemia

TABLE II

AGE INCIDENCE

Type of Leukemia	*Average Age Years* Men	Women	For Group
Lymphocytic	59 36	56 55	58 64
Aleukemic"	52 20	62	53 83
Granulocytic	51 91	65 33	58 68
Monocytic	54	–	54
Type not specified	–	–	–

TABLE III

AGE INCIDENCE ACCORDING TO DECADES

Type of Leukemia	*Lymphocytic*			*Aleukemic*			*Granulocytic*			*Monocytic*			*Not Given*			*Total for All Types*
Sex	*M*	*W*	*Total*	*M*	*W*	*Total*	*M*	*W*	*Total*	*M*	*W*	*Total*	*M*	*W*	*Total*	
Age Group																
10-19	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	1
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30-39	1	1	2	0	0	0	1	0	1	0	0	0	0	0	0	3
40-49	8	2	10	2	0	2	2	0	3*	0	0	0	0	0	0	15
50-59	17	10	27	2	0	2	3	1	4	1	0	1	0	0	0	34
60-69	15	3	18	1	1	2	3	1	4	0	0	0	0	0	0	24
70-79	11	1	12	0	0	0	2	1	3	0	0	0	0	0	0	15
80-89	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1
			70			6			16			1			0	93

*Sex Not Given

TABLE IV

LOCALIZATION OF HERPES ZOSTER

Region Involved	*Number of Cases*
Trunk	38
Head and neck	23
Upper extremities	6
Sacral area	4
Lower extremities	2
Not specified	32

TABLE V

SIDE OF BODY INVOLVED BY HERPES ZOSTER

Side	*Number of Cases*
Left	37
Right	22
Bilateral	1
Not specified	45

often contained several nuclei The majority of the cells were present in the cords The sinuses were narrow and often obscured by the swelling of the endothelial cells and the numerous cells in the lumen The trabeculae showed a moderate degree of activation of the cells, and the endothelium of the intratrabecular veins was often undermined by granulocytic and monocytic cells

Duration Among the 105 cases of herpes zoster associated with leukemia, the leukemia preceded the development of zoster in the majority of cases The zoster usually appeared between the second and third year following the development of leukemia (average 2 83 years) However, herpes zoster was the initial manifestation of the leukemic process in the patients reported by Freund (200b), Bafverstedt (21a) and Koyenburg (339) All patients had the chronic form of leukemia except Bluefarb's (56a) patient who had acute monocytic leukemia

Sex Among the 105 patients who had leukemia associated with herpes zoster, 72 were men, 22 were women and the sex was not mentioned in 11 cases The sex distribution according to the type of leukemia present, is shown in Table I

TABLE I
SEX INCIDENCE

Type of Leukemia	*Men*	*Women*	*Sex Not Given*	*Total Cases*
Lymphocytic	52	18	4	74
'Aleukemic'	6	1	0	7
Granulocytic	12	3	2	17
Monocytic	1	0	0	1
Type not specified	1	0	5	6
TOTAL CASES	72	22	11	105

Age Among 93 cases in which the age was given the average age, according to the type of leukemia may be found in Table II

The average age for the entire group was 57 5 years for the men, 58 years for the women and for both sexes the average age was 57 43 years (Table III)

The age was not mentioned in 12 of the 105 cases The youngest patient was a 17 year old boy with granulocytic

Among the 105 cases reviewed here three patients had facial paralysis associated with herpes zoster and leukemia (Bafverstedt 21a Marques 433 and Tapie and Cassar 674) Facial paralysis may however, occur in leukemia without herpes zoster but this involvement is usually bilateral Cases having this association were described by May (439), Eisenlohr (162) Muller (464), Kast (331), Hellgardt (273), E Block and Hirschfeld (54) Lowy (400) and Garvey and Lawrence (212) Paralysis of an extremity occurred following herpes zoster in three cases Arzt s (16d) patient had paralysis of the left upper extremity following zoster and Pollock (533) suggested that leukemic infiltration of the anterior root ganglion might have occurred A patient reported by Wile and Holman (731f case 1) had paresis of the right arm which was believed to be secondary to leukemic infiltration of the cervical roots of the spinal cord The patient described by Carr (101) had paresis of the arm Forkners (192b) patient had loss of sensation and atrophy of the muscles over the area of distribution of the ulnar nerve and one patient reported by D Anderson (8) had paresthesia of the right lower leg

Leukemic Infiltrations in Healed Scars of Herpes Zoster Leukemic cutaneous infiltrations may follow healing of the lesions of herpes zoster Such involvement was described in 10 cases nine of whom had lymphocytic leukemia

According to Halle (255), various types of trauma may result in leukemic cutaneous infiltrations and herpes zoster because of its inflammatory character, may act similarly A patient who presented leukemic cutaneous infiltrations at the *sites of injections* and surgical incisions was reported by Cleland (115) Keim (333a) believed the lesions of herpes zoster to be merely a traumatic stimulus causing an influx of leukemic cellular infiltrates into the involved area D Anderson (8) described one patient who presented keloids in the scars of herpes zoster Other patients having leukemic infiltrations *in the scars* have also been reported Barney s (28c) patient was a 64 year old man with lymphocytic leukemia

Although herpes zoster appears to have no predilection for either the right or left side of the body an increased localization on the left side was apparent in this small series of cases

Arsenic Arsenic has frequently been noted to be the precipitating factor in herpes zoster Forkner *et al* (192d) suggested that arsenotherapy for leukemia might account for the occurrence of herpes zoster in some cases However this premise is not substantiated in the 105 cases reviewed here since only 22 (20 95 per cent) of these patients had arsenotherapy and five reports specifically mentioned that this drug had never been administered

Roentgenotherapy Roentgenotherapy was administered to 33 (31 42 per cent) of the patients in this series prior to the development of herpes zoster Nine (8 57 per cent) of these patients had received both arsenic and roentgenotherapy before the zoster appeared

Paralysis The logical assumption appears to be that the inflammatory changes present in the anterior horns of the spinal cord are due to the spread of the virus from the posterior horns of the spinal cord thus accounting for the occasional muscular paralysis occurring in a disease which principally affects the sensory system

Involvement of both the upper and lower motor neurons have been described The lower motor neurons are usually involved in facial paralysis as reported by Baird (22) Lowy (400) and Garvey and Lawrence (212) Occasionally deafness results from involvement of the geniculate ganglion *Herpes zoster oticus* with facial paralysis and acoustic symptoms was first described in detail by Hunt (300) The next most frequent involvement appears to be oculomotor paresis reported by Essen Moller (170) Friedreich (202) Carmody (99) and others Lower motor neuron paralysis is not a common complication involving the lumbar or sacral regions although Carter and Dunlop (102) described two patients who had herpes zoster of the lumbar region complicated by lower motor neuron paresis involving the affected segments

lymphocytic leukemia The 49 year old man, described by Anhalt and Forsey (11), had milia like cutaneous lesions in the healed areas of zoster approximately five months after the herpes zoster lesions had healed Histologic study of the skin disclosed a typical leukemic infiltrate

Case Report A 53 year old man first presented herpes zoster in the right posterior thoracic region two months previously These lesions which had been markedly painful, had regressed considerably but some still remained two months later and he continued to have pain in the anterior region of the right side of the chest He had a moderately severe infection of the upper respiratory tract for a period of two weeks and considerable coughing during this time Six weeks after the appearance of the herpes zoster he had redness of the right eyeball following exposure to "dust and wind" and several days later the left eyeball became similarly, but less severely, involved Two days later, swelling and reddish discoloration of both periorbital tissues developed On examination, he had slight bilateral dilatation of the cervical veins and severe bilateral subconjunctival ecchymoses which were most marked in the right eye where the entire sclera was infiltrated with blood There was a patchy ecchymosis of the left eye The upper and lower eyelids and the bilateral periorbital tissues were swollen and reddish-yellow in color, with cutaneous scaling of the overlying areas The liver was enlarged below the costal margin and the spleen extended to the iliac crest There were cutaneous vesicles and papules involving the distribution of the fifth and sixth thoracic nerves, the right paravertebral region and in the right axilla and nipple region He had generalized lymphadenopathy The sternal bone marrow studies disclosed typical lymphocytic cells and there were numerous blast cells Therapy consisted of intravenous injections of urethane, starting with 2 gm. and increasing to 10 gm He died three and one-

who had herpes zoster on the right side of the thorax A 52 year old man with lymphocytic leukemia who presented herpes zoster over the ophthalmic and maxillary branches of the right trigeminal nerve was described by Barton and O'Leary (31) On histologic examination, there was leukemic infiltration in the zosteriform lesion and in a solitary cutaneous lesion on the left side of the thorax Freund s (200b) patient, a 49 year old woman with lymphocytic leukemia, had herpes zoster on the left side of the head and neck followed by a generalized zosteriform eruption A 63 year old man with lymphocytic leukemia who had generalized herpes zoster, essentially the same as in Jadassohn's (313c) patient, was reported by Gottron and Jakobi (238c) Jadassohn's patient was a 68 year old man with lymphocytic leukemia associated with gangrenous herpes zoster of the first and second branches of the trigeminal nerve This eruption subsequently became generalized and several weeks later slightly elevated round infiltrates, as well as "pea" sized papules, occurred in the zoster scars and also in areas which had been involved with the varicelliform exanthem Histologic examination disclosed leukemic infiltrates in both areas of cutaneous involvement

Halle's (255) patient, a 71 year old man with lymphocytic leukemia, had *herpes zoster involving the right sacral* area the gluteal area and the upper part of the thigh A brownish red, firm, papular cutaneous eruption developed in the healed areas involved by the zoster which showed leukemic infiltrates, on histologic examination Katz (332) reported a 49 year old woman with lymphocytic leukemia who first presented herpes zoster on the right cheek and right side of the neck and thorax, extending down to the third rib This eruption later became generalized after healing leukemic infiltrates were demonstrated histologically in the zoster scars Wilkinson (732) reported a 52 year old man whose first symptom was herpes zoster in the region of the tenth dorsal segment on the left flank which had appeared three months' previously One month later, brownish purple, smooth cutaneous nodules and plaques appeared which were histologically typical of

enlargement of the abdomen and swelling and edema of the legs There were numerous excoriated cutaneous lesions on the arms and chest massive pitting edema of both lower extremities below the knees and marked splenomegaly The diagnosis was chronic granulocytic leukemia At autopsy two and one half years later there were granulocytic leukemic infiltrations of the lungs heart aorta spleen liver pancreas adrenal glands kidneys prostate testicles stomach, intestine lymph nodes and brain

Involvement of the Nervous System The possibility that a leukemic infiltration of the spinal ganglion may act as a "trigger factor" in activating the specific virus of herpes zoster has already been mentioned

The first reported case of generalized herpes zoster having the primary eruption over the fifth dorsal nerve on the right side was that of Fischl (186) At autopsy there was periganglionic leukemic infiltration with inflammatory changes within the ganglions involving both Gasserian ganglions most marked on the right side Fischl was unable to draw any conclusions regarding the causal relationship of the leukemic changes to the herpes zoster The patient reported by Freund (200b) had gangrenous zoster involving the third cervical nerve on the left side as well as a generalized vesicular cutaneous eruption At autopsy there were "inflammatory changes" in both third cervical ganglions and in the fourth and fifth left cervical ganglions as well as in their posterior roots The same changes were apparent in the second third and fourth cervical segments of the cord This relatively widespread nervous system inflammatory reaction is a frequent finding in herpes zoster not associated with leukemia However in this case there was a *hematoma* near the third cervical ganglion corresponding to the distribution of the primary herpes zoster which was considered to be a predisposing *factor for the localization of the zoster* virus Autopsy examination of Wohlwill's (741) patient disclosed a leukemic infiltration in both trigeminal roots but

half months later and at autopsy there was marked icterus of the skin, cellulitis of the ulnar surface of the right forearm and numerous hemorrhages in the cubital fossae, as well as moderate subcutaneous ecchymoses of the left groin and testicle The anatomic diagnoses were lymphocytic leukemia, focal necrosis of the liver secondary to urethane therapy, chronic splenitis secondary to leukemia, and mild atrophy of the testicles

Case Report A 47 year old man first presented pallor of the skin and mucous membranes but there were no cutaneous lesions One month later he had an acute vesicular cutaneous eruption involving the left anterior, lateral and posterior regions of the chest Five days previously he had noted neuralgia like pains of the chest which were followed by the appearance of numerous 1 0 mm to 0 5 cm vesicles which tended to coalesce These lesions involved the distribution of the third to fifth ribs Ten days later he had markedly severe herpes zoster in the left intercostal region, just below the nipple, and extending around the trunk There were also varicelliform cutaneous lesions on the posterior and anterior areas of the trunk and face Nine months later examination disclosed a few small discrete hemorrhagic lesions on the extremities He died two weeks later and autopsy revealed lymphocytic leukemia

Keyenburg (339) reported a 75 year old man who had herpes zoster associated with granulocytic leukemia Histologic examination of the zoster lesions disclosed leukemic infiltration

Case Report A 52 year old Negro presented cutaneous pigmentation resulting from herpes zoster in the region of the ninth and tenth ribs on the right side He had dyspnea and edema of the joints and extremities During the preceding four years he had noted intolerance to heat, shortness of breath and dyspnea on exertion For the previous three years there had been

view that herpes zoster may result from leukemic infiltration of the posterior root ganglion He presumed that a *locus minoris resistentiae* was produced by leukemic changes when the specific zoster localized and disseminated He also suggested that, as in Milian's nine day erythema, the local tissue immunity was lowered and the herpes zoster virus was then able to initiate specific changes

Wohlwill (741) performed histologic studies to determine whether lesions of the spinal ganglion could cause herpes zoster He studied the entire peripheral nervous system in six cases of idiopathic zoster and in four cases of secondary zoster due to gastric carcinoma, lymphosarcoma, lymphocytic leukemia and syphilis He found that involvement of the spinal ganglia was not constant in either type of herpes zoster In the case caused by carcinomatous infiltration of the anterior branch of an intercostal nerve, he found that the dorsal ganglia were intact In another case, the posterior root of the peripheral nerve was involved and in another the posterior horn of the spinal cord was involved, but the dorsal ganglia were not affected Wohlwill concluded that herpes zoster can be produced by involvement of any point of the afferent portion of the reflex arc However, the dorsal ganglion remained the most frequent point of involvement Trommer and Wohlwill (689) did histologic studies of the nervous system in 12 cases of leukemia They found leukemic involvement of the Gasserian ganglion in four of nine cases in which this ganglion was studied None of these patients had herpes zoster, despite involvement of the Gasserian ganglion

There are several reports of paresis occurring with leukemia in which herpes zoster did not appear Lowy (400) presented a 47 year old woman in whom total paresis of the right facial nerve had suddenly developed in addition to excessive salivation and partial deafness in the right ear Two weeks later severe pain occurred in the region of the right ear She had faucial angina and an abscess on the right tonsil which ruptured on examination The hemogram was char-

there was no involvement of the Gasserian ganglions In Scheinker's (603) patient, autopsy revealed leukemic infiltration around the bilateral portion of the nerve roots and in the upper eight dorsal nerves of the spinal ganglia The herpes zoster lesions were unilateral in this case, and the leukemic changes were considered to be a predisposing factor in the localization of the zoster virus and not a direct cause of the cutaneous lesions

Damm (140) described a patient who had generalized herpes zoster with leukemic infiltrates in the second thoracic and third lumbar segments of the portion of the spinal cord which was examined These changes were most marked in the lumbar segment which corresponded to the distribution of the primary herpes zoster and there was a diffuse lymphocytic infiltration around the entrance of the posterior roots of the spinal nerves Damm believed that the leukemic changes acted as a predisposing factor for the localization of the herpes zoster virus

In the case of monocytic leukemia reported by Bluefarb (56a), autopsy disclosed leukemic monocytic cells involving the left seventh spinal ganglion and the sixth and seventh left intercostal nerves

Three patients who had acute lymphocytic leukemia with facial paralysis were described by Garvey and Lawrence (212) Two patients had bilateral involvement and one unilateral involvement At autopsy, one case showed lymphocytic infiltration of the facial nerves and some degenerative changes in the nerve tissue This patient had infiltration of the nerves with resulting paralysis, prior to the increase of peripheral white blood cells These patients did not have herpes zoster, however

In a study of the spinal fluid of leukemic patients having herpes zoster, Marigonda (430) observed an increase of leukocytes similar to those in the peripheral blood and he concluded that the spinal ganglion was affected in these cases However, Cole (118) found no conclusive evidence for the

cutaneous eruption and severe varicella is not always possible However histologic differentiation is possible according to Philadelphy and Haslhofer (519) They described the typical histologic picture of varicella as showing innumerable "multi nucleated giant cells" in the epidermis swelling of the endothelial cells and the escape of inclusion bodies in the nucleus of the epithelial cells Many vesicular cutaneous eruptions may possibly be unusual types of varicella which can be dif ferentiated only by histologic study

The confusion regarding varicella and herpes zoster gen eralisatus associated with leukemia is illustrated in the follow ing cases

1 Bafverstedts (21a) patient had a cutaneous eruption which simulated varicella so closely that this diagnosis would have been logical had not the disease begun as a localized herpes zoster

2 Dostrowsky (150) reported a child who had varicella 25 days after the father had an eruption of herpes zoster

3 Two distinct diseases occurred in a 17 year old boy described by Holbrook (290) He had varicella as well as lymphocytic leukemia The vesicular lesions of varicella ap parently had a localizing effect on the cutaneous invasion of the leukemia Holbrook believed and the atypical course of the varicella undoubtedly resulted from the leukemia He gave a comprehensive review of the literature regarding the relationship of herpes zoster and varicella

4 Marcus (427) mentioned two patients who had general ized herpes zoster and leukemia simultaneous to an epidemic of varicella

5 A 4 year old boy described by Parkes Weber (502a) had varicella 10 days after having been hospitalized in a ward with a patient who had herpes zoster

6 Philadelphy and Haslhofers (519) patient, a 51 year old man with chronic lymphocytic leukemia had a vesicular cutaneous eruption which was believed to be gangrenous varicella Histologic study of the vesicles revealed the typical

acteristic of lymphocytic leukemia Autopsy disclosed the facial nerve to be infiltrated by a deposit of lymphoid tissue in the petrous portion of the temporal bone

Herpes Zoster Generalisatus. In addition to the zonal distribution of the lesions, there may be aberrant cutaneous vesicles which have been reported to range from five to 30 in number Tenneson (678) found these "vesicle aberrants" to be present in 90 per cent of patients having herpes zoster Among 30 consecutive cases of herpes zoster, Bluefarb and Morris (56g) found that 20 (66 per cent) had aberrant vesicles

A more infrequent occurrence is reported to be herpes zoster generalisatus Among the 105 cases in our series, 51 (48 57 per cent) presented generalized herpes zoster This may have been due to the advanced age of the patients and to the lowered resistance resulting from the presence of leukemia In many cases this lowered resistance was apparent in that the vesicular lesions tended to become hemorrhagic, gangrenous and necrotic However, generalized zoster eruptions occur more frequently in association with leukemia than with other diseases

Herpes Zoster Generalisatus Versus Varicella The results of epidermiologic studies indicate that normal persons who are exposed to herpes zoster may develop chicken pox, and zoster may also occur in persons exposed to chicken pox

Vesicular cutaneous eruptions may also be associated with lymphocytic leukemia as in the cases described by Paltauf (499a), Arzt and Fuhs (16e), Ormsby (494c), Bertaccini (44a), S K Rosenthal (579), Kreibich (355b), Mariani (429), Balassa (24), Ambrogio (6), M Wolf and Gounelle (742), Chatellier and Sorel (111) Oppenheim (492), Parkes Weber (502c), Sachs (592), Rille (564) and P I MacCallum (412) Similar vesicular eruptions have been described in cases of granulocytic leukemia by Hudelo *et al* (299), Schultze and Schnitter (613b) and Rodnan and Rake (570)

A clinical differential diagnosis between a leukemic vesicular

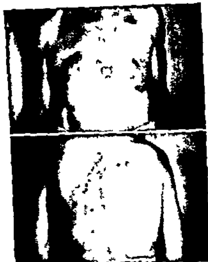


Figure 91 Bilateral herpes zoster associated with chronic leukemia

ular cutaneous lesions on the buttocks However, the recurrent nature of the lesions made a diagnosis of herpes simplex more plausible in this case Keining's (334) patient had marked lymphadenopathy and the peripheral white blood cells numbered 43 000 per cu mm, with 59 per cent lymphocytes The lymphadenopathy disappeared 12 days later and the white blood cell count was 7,000 per cu mm Marques (433) considered this patient to have herpes zoster associated with leukemia However, herpes zoster with a leukemoid reaction appears to be a more accurate diagnosis Goldman (232) described a similar case This patient had varicella with a peripheral blood picture simulating leukemia but the hemogram showed normal findings 33 days later

Herpes Zoster Associated with Other Findings The patient reported by Gelfand (219) had enlargement of the parotid glands, orchitis due to viral mumps involving the left side, as well as herpes zoster Bosworth (67) described a patient who had Mikulicz's disease associated with herpes zoster and L

picture of varicella However a primary zoster was not established in this case and it could not be considered as an example of herpes zoster generalisatus

7 Rodman and Rake (570) reported a 57 year old man who had chronic lymphocytic leukemia He first presented herpes zoster which was followed eight days later by a generalized varicelliform eruption Study of the fluid from the disseminated vesicles by means of an electron microscope disclosed particles indistinguishable from those previously demonstrated in the herpes zoster lesions They suggested that herpes zoster with a varicelliform eruption has the same virus as that responsible for the primary zoster lesion and the subsequent disseminated varicelliform eruption They believed that this condition should therefore be designated as generalized or disseminated herpes zoster

Questionable Cases Abramowitz (1c) reported a 55 year old man with lymphocytic leukemia who had recurrent vesic-



Figure 89 Varicelliform eruption following herpes zoster

Figure 90 Close up of lesions in Figure 89

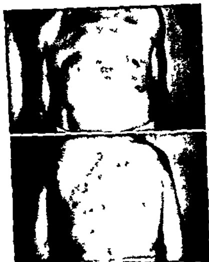


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Figure 89 Varicelliform eruption following herpes zoster

Figure 90 Close up of lesions in Figure 89

mg/100 cc non protein nitrogen 9 2 units/100 cc (Bodansky) alkaline phosphatase and 2 02 units (MacLagen) gamma globulin turbidity Examination of the sternal bone marrow was reported to show abnormal marrow compatible with the clinical diagnosis" (chronic lymphocytic leukemia)

Case Report A 72 year old man first noted inguinal lymphadenopathy Four years later he was admitted to the hospital because of severe weakness and arthralgia of both legs He was found to have congestive heart failure and malnutrition as well as chronic lymphocytic leukemia Therapy consisted of roentgen rays digitalis codeine Mulcin® and a low sodium diet Four months later he was again admitted to the hospital At that time he presented herpetiform cutaneous lesions which had been present for 10 days This markedly painful eruption involved the sciatic nerve on the



Figure 93 Zoster involving the left thigh (case report)

Figure 94 Zoster on left leg and foot (case report)

Frank's (196) patient also had encephalitis and herpes zoster Kuta (363) reported a patient who had bilateral and symmetrical herpes zoster with involvement of the ophthalmic branch of the trigeminal nerves

We have recently observed two additional cases of herpes zoster associated with lymphocytic leukemia

Case Report This 70 year old man first presented a "sore" and cutaneous scaling over the right side of the upper lip following pneumonia three years' previously He also had lymphadenopathy in the right submandibular region The cutaneous nodule was believed to be malignant and was removed by surgery A diagnosis of 'lymphoblastoma" was made after histologic study of this lesion At the time of examination he had markedly painful, erythematous, vesicular cutaneous lesions on the right flank which had been present for approximately six weeks There were generalized discrete varicelliform cutaneous lesions which were most marked on the trunk and had been present for two weeks The hemogram revealed 6,600 white blood cells per cu mm, with 38 per cent polymorphonuclears, 8 per cent band forms, 2 per cent eosinophils, 51 per cent lymphocytes and 1 per cent monocytes Biochemical examinations disclosed 48



Figure 92 Zoster involving one side of the penis Marked inguinal lymphadenopathy (case report)

I LYMPHOCYTIC LEUKEMIA

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
1	D Anderson (8)	65	M		Right	Chest	Paresthesia right lower leg	Yes				Organic lesion in vertebral canal at fourth right thoracic segment Keloids over healed zoster scars
2	D Anderson (8)	58	M		Left	Severe, first and second lumbar segments					Radioactive phosphorus	Patchy leukemic cutaneous infiltrations of legs Zoster lesions became ulcerated
3	Anhalt and Forsey (11)	49	M		Left	Ophthalmic and frontalis with corneal involvement						Milia like cutaneous lesions developed in healed zoster lesions five months later. Histologic study showed a leukemic infiltrate



Figure 95. Zoster on sole of left foot (case report).

left side and extended to the left sole. The hemogram revealed 75 per cent hemoglobin, 3,800,000 red blood cells and 115,800 white blood cells per cu. mm., with 94 per cent lymphocytes. Biochemical studies disclosed 41 mg/100 cc. non protein nitrogen, 102 mg/100 cc. total cholesterol and the icterus index was 8 units.

The following table offers a brief summary of the 105 cases of leukemia associated with herpes zoster which we have reviewed However, there are undoubtedly many more cases of this association which have been observed but not recorded in the literature.

12	Bluefarb	53	M	3½ Months	Right	Posterior thoracic region	No	No	No		Urethane	Focal necrosis of liver following urethane therapy
13	Bluefarb	47	M	10 Months	Left	Third and fifth rib distribution	No	Yes				Herpes zoster with generalized varicelliform cutaneous eruption
14	Bluefarb	70	M	3 Years	Right	Flank Ninth thoracic segment	None	Yes				
15	Bluefarb	72	M	4 Years	Left	Lower extremity Sciatic nerve First, second and third sacral segments	None			Yes		
16	Bosworth (67)	43	M		Left	Tenth, eleventh and twelfth thoracic, first and second lumbar segments		Yes		Yes		Cutaneous ulcers from zoster Leukemia cutis. Mikulicz's disease
17	Brandt (73)	72	M	1 Year	Right	Fourth fifth and sixth dorsal segments		Yes		Yes		

1 LYMPHOCYTIC LEUKEMIA (continued)

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
4	Arzt (16d)	63	F	'Years'	Right	Over and under upper arm	Paralysis of arm	Yes	Yes	Yes		
5	Bafverstedt (21a)	70	M	Several months			Paralysis of face	Yes	No			
6	Baldridge and Awe (25a)											
7	Bancroft and Mac-Eachern (26)	60	M					Yes				
8	Barney (28c)	64	M	2½ Years	Right	Ninth and tenth dorsal segments				Yes		Leukemic infiltrate in zoster scars
9	Barton and O Leary (31)	52	M		Right	Ophthalmic and maxillary branches trigeminal nerve		Yes				Leukemic infiltrate in zoster scars
10	F T Becker (37b)	60	M		Right	Inguinal region and thigh		Yes				Large bullous lesions
11	Bluefarb	55	M		Left	Third sacral segment		Yes				

26	Ehrmann (160)	45	M									Tumors in zoster ganglion Scarring present
27	Fischl (186)	61	M		Right	Neck and back of ear to *sternum*						Leukemic infiltration of Gasserian ganglion
28	Forkner (192B)	58	M	2½ Years	Left	Supraclavicular region and anterior nerve roots	Loss of sensation and atrophy of muscles over area of distribution of ulnar nerve		No	*No*	*No*	
29	L. Frank (196)	58	M		Right	Cervical region		Yes		Yes	Urethane	Encephalitis
30	Freund (200B)	57	F	2 Months	Left	Sides of neck and scalp		Yes				
31	Geiger (217)											

1 LYMPHOCYTIC LEUKEMIA (continued)

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
18	Brunauer (78)	52	M	2 Years	Right	Second and third dorsal segments			Yes	Yes		
19	Brunauer (78)	52	F	3 Years	Right	Thorax			Yes	Yes		
20	Buschke (87A)	55	M		Left	Arm		Yes				
21	Catlin (105)	25	M		Left	Tenth dorsal segment						Leukemic infiltration at site of zoster
22	Cornbleet et al (123A)	81	F			Fourth and fifth thoracic vertebral segments		Yes	No			Gangrenous zoster
23	Cornil and Paillas (125)	52	M		Left	Intercostal region		Yes		Yes		
24	Damm (140)	65	M					Yes				
25	Dostrowsky (150)	55	M	2 Years		Second, third and fourth dorsal segments		Yes	Yes			

38	Jadassohn (313C)	68	M			First and second branch trigeminal nerve		Yes				
39	Jadassohn (313A)	71	M	2 Years		Sacral and gluteal areas			Yes	Yes		
40	Jadassohn (313A)	37	F	5 Years	Left	Head and neck				Yes		
41	Kalz (324)	54	F			Thoracic region			Yes			
42	Katz (332)	49	F	1 Year(?)	Right	Cheek neck and chest to third rib		Yes				
43	Kreibich (355C)	70	M		Right	Lumbar region		Yes				
44	Kuta (363)	60	F			Bilateral ophthalmic branches trigeminal nerve			Yes			Generalized varicelliform cutaneous eruption
45	Lepp (381)	59	F		Left	Second to fifth dorsal segments		Yes				
46	Lynch (409A)	48	M	3 Years	Left	Posterior thoracic region		Yes	Yes	Yes		
47	MacCallum (412)	67	M		Left	Third, fourth fifth cervical segments						Varicelliform cutaneous eruption

1 LYMPHOCYTIC LEUKEMIA (continued)

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
32	Gelfand (219)	70	M		Left	Scalp, frontal region		Yes				Hemorrhagic Swelling of both and orchitis on left side due to parotid glands viral mumps Keratitis, scleritis, loss of vision left eye
33	Glaubersohn (227)	52	F	3 Years	Left	Thoracic region		Yes				
34	Gottron and Jakobi (238C)	63	M	Years		Third and fourth cervical segments		Yes				
35	Haack (248)	67	F	1 Year	Left	Face and neck (fifth nerve)		Yes	No			
36	Hallgren (256)	64	M			Generalisatus		Yes				
37	Hallgren (256)	66	M			Fourth thoracic segment						

38	Jadassohn (313C)	68	M			First and second branch trigeminal nerve		Yes				
39	Jadassohn (313A)	71	M	2 Years		Sacral and gluteal areas			Yes	Yes		
40	Jadassohn (313A)	37	F	5 Years	Left	Head and neck				Yes		
41	Kalz (324)	54	F			Thoracic region			Yes			
42	Katz (332)	49	F	1 Year(?)	Right	Cheek neck and chest to third rib		Yes				
43	Kreibich (355C)	70	M		Right	Lumbar region		Yes				
44	Kuta (363)	60	F			Bilateral ophthalmic branches trigeminal nerve			Yes			Generalized varicelliform cutaneous eruption
45	Lepp (381)	59	F		Left	Second to fifth dorsal segments		Yes				
46	Lynch (409A)	48	M	3 Years	Left	Posterior thoracic region		Yes	Yes	Yes		
47	MacCallum (412)	67	M		Left	Third fourth fifth cervical segments						Varicelliform cutaneous eruption

1. LYMPHOCYTIC LEUKEMIA (*continued*)

Case	*Reported by*	*Age*	*Sex*	*Duration of Leukemia*	*Involvement by Zoster*		*Associated Nervous Signs*	*Generalized*	*Previous Therapy*			*Other Findings*
					Side	*Site*			*Arsenic*	*Roentgen*	*Other*	
48	MacCallum (412)	75	M		Left	First and second lumbar segments				Yes		Hemorrhagic, varicelliform cutaneous lesions
49	Marcus (427)	72	M			Fourth and fifth dorsal segments		Yes				
50	Marques (433)	76	M		Left	Head and neck	Paralysis of face	Yes	No			
51.	Munsterer (465)	45	M	3 Years	Left	Occipital region		Yes	Yes			
52	Murphy (466)	55	F							Yes		Zoster followed "spray" roentgenotherapy
53	Murphy (466)	70	F							Yes		Zoster followed "massive" doses roentgenotherapy
54	Murphy (466)	61	M							Yes		Zoster followed "massive" doses roentgenotherapy

55	Nanta (470C)	66	M	2 Years								
56	Parounagian (504)	52	F			Pectoral region		Yes	Yes			Gangrenous zoster
57	*Parkes-Weber* (502A)	59	M	2 Years	Right	Shoulder		Yes	Yes			Arsenotherapy two weeks prior to zoster
58	Parkhurst (503)	49	F	2 Years	Right	Shoulder, arm, forearm, *third* to sixth cervical segments		Yes	Yes			
59	Proebsting (540)							Yes	Yes	Yes		
60	Proppe (541)							Yes				
61	Rodnan and Rake (570)	57	M	10 Years	*Right*	*Chest* wall, ninth thoracic segment		Yes		Yes	Urethane and transfusions whole blood	Necrosis at site of zoster Generalized varicelliform cutaneous lesions eight days after zoster appeared
62	Rosenow (577)	49	M	4 Years		Region of sciatic nerve				Yes		

1. LYMPHOCYTIC LEUKEMIA (*continued*)

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
48.	MacCallum (412)	75	M		Left	First and second lumbar segments				Yes		Hemorrhagic, varicelliform cutaneous lesions
49.	Marcus (427)	72	M			Fourth and fifth dorsal segments		Yes				
50.	Marques (433)	76	M		Left	Head and neck	Paralysis of face	Yes	No			
51.	Munsterer (465)	45	M	3 Years	Left	Occipital region		Yes	Yes			
52.	Murphy (466)	55	F							Yes		Zoster followed "spray" roentgenotherapy
53.	Murphy (466)	70	F							Yes		Zoster followed "massive" doses roentgenotherapy
54.	Murphy (466)	61	M							Yes		Zoster followed "massive" doses roentgenotherapy

55	Nanta (470C)	68	M	2 *Years*								
56	Parounagian (*504*)	52	F			*Pectoral region*		Yes	Yes			Cangrenous zoster
57	*Parkes-Weber* (502A)	59	M	2 Years	Right	Shoulder		Yes	Yes			Arsenotherapy *two weeks* prior to zoster
58	Parkhurst (503)	49	F	2 Years	Right	Shoulder, arm, forearm, third *to sixth cervical* segments		Yes	Yes			
59	*Proebsting* (540)							Yes	Yes	Yes		
60	Proppe (541)							Yes				
61	Rodnan and Rake (*570*)	57	M	10 Years	Right	Chest wall, ninth thoracic segment		Yes		Yes	Ure-thane *and* trans-fusions whole blood	Necrosis at site of zoster. Generalized varicelliform cutaneous lesions eight days after *zoster* appeared
62	Rosenow (*577*)	49	M	4 Years		Region of sciatic nerve				Yes		

I LYMPHOCYTIC LEUKEMIA (continued)

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
63	Scheinker (603)	52	F	3 Years	Right	Second to seventh dorsal segments			Yes	Yes		
64	Schlesinger (607)	70	M			Region of hip						
65	Schlesinger (607)	56	F			Fifth to ninth dorsal segments						
66	Skeer (636A)	40	M	2 Years	Left	Fifth lumbar, first sacral segments		Yes		Yes		
67	Skeer (636A)	53	F	1 Year	Right	Head		Yes		Yes		
68	Sparling et al (645)	56	M		Left	Upper quadrant abdomen		Yes				Mucous membranes involved At autopsy, infiltration of lymphocytes, plasmacytes and monocytes in spinal ganglion no leukemic cells

69	Tiessen (683)	67	M					Yes				
70	Wile and Holman (731F)	58	M	2 Years	Left	Forearm and arm	Paresis left arm	Yes		Yes		
71	Wile and Holman (731F)	52	M	15 Months	Right Left	Fronto parietal area and upper extremity		Yes		Yes		
72	Wilkinson (732)	52	M		Left	Tenth dorsal segment						Brownish purple *cutaneous nodules* and plaques followed *zoster* Histologic study of nodule revealed leukemic deposits supervening on zoster
73	Wohlwill (741)	35	M		Left	Cheek						
74	Ziel (752)	67	M	"Long period"	Left	Breast, corresponding at same height in dorsal area		Yes				

2 "ALEUKEMIC" LEUKEMIA

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
75	Brandt (73)	50	M	9 Years				Yes		Yes	Radium	
76	Craver and Haagensen (130D)	47	M	1 Year	Left	Eleventh dorsal segment				Yes		
77	Lehner (378)	62	F		Left	Supraorbital region			Yes		Potassium iodide	
78	Marcus (427)	55	M			Third branch trigeminal nerve		Yes	Yes			
79	Norden (483)	45	M	9 Years	Right	Forehead and over eye		Yes		Yes		
80	Stohr and Holscher-Immisch (656)	64	M	5 Years	Right	Chest			Yes			Gangrenous zoster
81	Strobel (660)		M					Yes				

3 GRANULOCYTIC LEUKEMIA

82.	Bluefarb	52	M	2½ Years	Right	Ninth and tenth ribs		Yes				Cutaneous pigmentation following zoster
83	Carr (101)	50	M		Left	Arm forearm, shoulder	Paresis of arm		Yes	Yes	Benzol	
84	E Epstein and MacEachern (166)											
85	A Frank (195)	48	M		Left	Shoulder, breast, back, third to fifth cervical segments					Urethane	
86	Freund (200B)	40			Left	Angle jaw and part of neck, third cervical segment				Yes		
87.	Hallgren (256)	60	M			Throat						
88	Hallgren (256)	17	M									
89	Hallgren (256)	60	M									

2 ALEUKEMIC LEUKEMIA

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Generalized	Previous Therapy			Other Findings
					Side	Site			Arsenic	Roentgen	Other	
75	Brandt (73)	50	M	9 Years				Yes		Yes	Radium	
76	Craver and Haagensen (130D)	47	M	1 Year	Left	Eleventh dorsal segment				Yes		
77	Lehner (378)	62	F		Left	Supraorbital region			Yes		Potassium iodide	
78	Marcus (427)	55	M			Third branch trigeminal nerve		Yes	Yes			
79	Norden (483)	45	M	9 Years	Right	Forehead and over eye		Yes		Yes		
80	Stohr and Holscher-Immisch (656)	64	M	5 Years	Right	Chest			Yes			Gangrenous zoster
81	Strobel (660)		M					Yes				

97	Murphy (466)	73	F							Yes		Zoster followed roentgenotherapy
98	Tapie and Cassar (674)	57	M			First to fourth cervical segments	Facial paralysis					
4 MONOCYTIC LEUKEMIA												
99	Bluefarb (56A)	54	M		Left	Chest			No			
5 TYPE NOT SPECIFIED												
100	Schwab and Weiss (614)											Found four (6 per cent) of 69 cases of leukemia had herpes zoster
101	Schwab and Weiss (614)											
102.	Schwab and Weiss (614)											
103	Schwab and Weiss (614)											
104	Spiegler (646)		M	15 Months	Left	Intercostal region			Yes	Yes		
105	Zeisler (750A)							Yes				

3 GRANULOCYTIC LEUKEMIA (*continued*)

Case	Reported by	Age	Sex	Duration of Leukemia	Involvement by Zoster		Associated Nervous Signs	Gen eral t ed	Previous Therapy			Other Findings
					Side	S te			Ar senic	Roent gen	Other	
90	Hynes (306 Case 8)	58	F									"Aleukemic" granulocytic leukemia
91	Kandel and Leroy (325B)	30	M						Yes			Zoster developed after six months of arsenotherapy
92	Kandel and Leroy (325B)	40	M						Yes			Zoster developed after three months of arsenotherapy
93	D Y Keith (336)	62	M		Left	Intercostal nerve						
94	Keyenburg (339)	75	M							Yes		Zoster preceded leukemia Leukemic infiltrations
95	Marigonda (430)	72	M					Yes				
96	Murphy (466)	65	F							Yes		Zoster followed roentgenotherapy

97	Murphy (406)	73	F							Yes	Zoster followed roentgenotherapy
98	Tapie and Cassar (674)	57	M			First to fourth cervical segments	Facial paralysis				
	4 MONOCYTIC LEUKEMIA										
99	Bluefarb (56A)	54	M		Left	Chest			No		
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102	Schwab and Weiss (614)										
103	Schwab and Weiss (614)										
104	Spiegler (646)		M	15 Months	Left	Intercostal region			Yes	Yes	
105	Zeisler (750A)							Yes			

4 Exfoliative Erythroderma

Exfoliative dermatitis (56c) is defined as a universal or extremely extensive exfoliation of the skin associated with inflammatory redness which varies from bright to dull red dusky violaceous or even of a yellowish tint There may be associated pruritus secondary pyoderma with exudation or fissuring accompanied by systemic manifestations or dehydration toxemia or hypoproteinemia The patient becomes extremely sensitive to external temperature changes especially cold and to pressure and friction The skin becomes dry and loses its normal elasticity There may be loss of nails and hair and when the disturbance is unusually severe atrophy of the skin may occur



Figure 96 Exfoliative dermatitis in a patient with lymphocytic leukemia (*A M A Arch Dermat* 73 189 1956)

Two types of exfoliative dermatitis known as the "Wilson Brocq type and pityriasis rubra of Hebra" are described in the older literature It is doubtful if these types actually represent clinical entities since cases formerly assigned to these types were reclassified as knowledge of exfoliative dermatitis

increased It is not possible to make a clinical distinction between the fully developed "Wilson Brocq" type and exfoliative reactions due to other diseases "Pityriasis rubra of Hebra" appears to describe exfoliative dermatitis associated with lymphomatous diseases This fact was noted by Pusey (542b) and Arndt (14b)

Two patients reported by Barney (28a) had exfoliative dermatitis which resembled "pityriasis rubra of Hebra" and proved to be a manifestation of lymphocytic leukemia He was of the opinion that this designation should not be used

Synonyms

1 Lymphadenosis cutis universalis (Arndt)
2 Lymphadenomatous erythroderma
3 Exfoliative dermatitis

Symptoms The subjective symptoms of exfoliative dermatitis are varied Frequently there are no subjective symptoms, as in some cases of exfoliative psoriasis or pityriasis rubra pilaris More frequently, however, pruritus is a prominent symptom in the majority of patients having cutaneous exfoliation from any cause The most frequent complaint is general "tenderness" of the skin associated with pruritus, and paresthesias may be present Temperature changes exaggerate the discomfort, and cool or moving air is not tolerated because of the excessive loss of body heat through radiation from dilated superficial blood vessels There is often a sensation of chilliness due to a more rapid loss of heat from the erythematous and inflamed skin than normally occurs

There may also be various general symptoms such as diarrhea fever headache malaise, or lassitude, depending upon the cause of the condition and the severity of the process The skin often has a "musty" odor

The objective findings depend almost entirely on the cause of the patient's cutaneous disease, according to Kierland (340) The reactivity of the skin varies markedly All gradations of cutaneous involvement may be present, from acute scarlatiniform erythema of dermatitis medicamentosa (due to barbiturate or quinine) to dull erythematous, dense lichenifi-

4. Exfoliative Erythroderma

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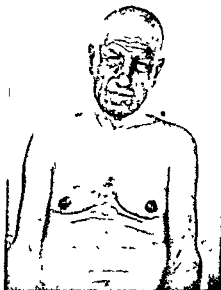


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Two types of exfoliative dermatitis known as the "Wilson-Brocq" type and "pityriasis rubra of Hebra" are described in the older literature It is doubtful if these types actually represent clinical entities, since cases formerly assigned to these types were reclassified as knowledge of exfoliative dermatitis

and involve a large part of the cutaneous surface Hypoproteinemia often develops from the loss of protein either by shedding of the scales or by exudation of serum The basal metabolic rate is usually elevated due to loss of heat from the cutaneous surface (340)

Lymphocytic Leukemia One of the most frequent non specific as well as specific cutaneous lesion which occurs in chronic lymphocytic leukemia is universal exfoliative erythroderma Erythroderma was associated with lymphocytic leukemic cutaneous infiltrations in 12 per cent of the 289 cases of leukemia reviewed by Beek (39a) When this manifestation occurs it is particularly significant since the cutaneous lesions may consist of fine branny scaling pigmentation or there may be evidence of thinning or atrophy symptoms characteristic of the condition formerly designated "pityriasis rubra (Hebra)" The majority of contemporary investigators share the opinions of Audry (18) and Nanta (470d) that the condition designated pityriasis rubra of Hebra" is merely a highly malignant form of leukemia or "aluekemic" erythroderma It has frequently been suggested that this designation be deleted from the literature and Jadassohn (313b) and Nicolau (479b) were convinced that "pityriasis rubra" should be included in the "leukemia group" of diseases However a critical analysis of Hebra s cases was not possible since no adequate or accurate hematologic studies were done According to Pusey (542a) the term "pityriasis rubra of Hebra" should now be discarded although formerly the differentiation between this condition and that produced by leukemia was not known Senear (624c) mentioned a patient who had been presented by Ormsby (494a) as an example of pityriasis rubra of Hebra However one year later Wile (731d) presented this same patient who then had a peripheral blood picture typical of leukemia

Exfoliative erythroderma or exfoliative dermatitis may occur in the "aleukemic" or leukemic phase of chronic lymphocytic leukemia All contemporary hematologists apparently agree that there is no fundamental difference between the leu

cation of chronic neurodermatitis (atopic dermatitis) The earliest visible cutaneous changes are erythema and slight edema The eruption usually develops with patches of red ness in the large folds of the body and spreads until it has nearly or completely covered the cutaneous surface Pressure with the finger tip reveals dilatation of the entire superficial vascular system with only the most transient pallor

Exfoliative dermatitis caused by sensitivity to local or internal medication is usually acute, with the development of an acute brilliant erythema The dermatitis develops fully within a few days to two weeks' time, after which the red ness becomes duller, exfoliation begins, and the dermatitis gradually regresses Exudation of serum from the acutely inflamed skin may appear at the height of the process on the lower extremities, face, ears and, when there is a local reaction, at the site of application of medication, according to Kierland (340)

The dermatosis assumes a chronic character when the exfoliative reaction is a part of an extension of specific cutaneous disease or when secondary to systemic disease The skin then has a dull red hue, is frequently lichenified and presents varying degrees of scaling The type of scaling is usually not characteristic but is sometimes suggestive, as in cases of pemphigus foliaceus The skin is usually dry but may become moist, especially in the body folds and on the sides of the trunk Eventually the skin becomes markedly infiltrated and the normal markings exaggerated

The cutaneous appendages are involved early in the disease There may be a temporary loss of hair and the nails frequently become opaque, lusterless, brittle, furrowed and soft, lose their attachments and are gradually shed Infiltration of the skin around the eyes may result in ectropion The palms and soles may remain normal but are frequently thickened, fissured and painful There is usually generalized lymphadenopathy and the mucous membranes may show an inflammatory reaction Exudation of serum with secondary crusting may occur in chronic types of universal exfoliation

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Exfoliative erythroderma or exfoliative dermatitis may occur in the "aleukemic" or leukemic phase of chronic lympho cytic leukemia All contemporary hematologists apparently agree that there is no fundamental difference between the leu

kemic and "aleukemic" phases of this disease This distinction is quantitative rather than qualitative, since the macroscopic as well as the microscopic changes are similar in both so called phases of the disease Leukemic erythroderma is characterized by cutaneous involvement consisting of subacute or chronic progressive "reddening" or erythema accompanied by exfoliation which varies from fine scaling, flaky or bran like, to large "leaf-like" areas of skin This dermatitis usually appears first as a "patchy" dermatitis in the inguinal or axillary folds and gradually spreads to involve the entire cutaneous surface However, generalized involvement does not always occur. In some cases only part of the cutaneous surface is involved and the eruption may simulate psoriasis or, occasionally, parakeratosis psoriasiforme, as described by Gate and Cullerct (213a) The skin may become thickened, particularly on the face where the accentuated folds produce a leonine facies, or the skin may become thinned and atrophic, causing retraction such as occurs in ectropion of the eyelids, as in a patient described by Keim (333c case 13) He also reported the occurrence of discrete and confluent papillomatous lesions which later developed into hypertrophic warty lesions

Subjective symptoms, such as "chilliness" due to increased loss of heat, intense pruritus, and secondary pyoderma, due to scratching, may occur Trophic changes, such as nearly complete alopecia were described by Ketron and Gay (338a), Rauschkolb and Freeman (549) and Keim (333c case 13), and the nails may become 'cracked' and thickened, as in Ketron and Gay s patient Fever usually occurs and superficial lymphadenopathy is invariably present with exfoliative erythroderma

Riehl (561) first described leukemic erythroderma in 1893 His patient, a 57 year old woman, had a "bright red' skin which was "glossy' in some areas while in others there was slightly branny scaling and in still other areas, there was excoriation There was marked cutaneous thickening of the inguinal regions and neck and the facial involvement simu-



Figure 97 Close up of patient in Figure 96

ated leonine facies

In 1914 Bernhardt (43) reported seven cases of leukemia with cutaneous involvement One of his patients (case 1) was a 57 year old woman who had generalized reddening and thickening of the skin, with abundant scale formation and areas of atrophy and warty lesions Since this patient also had cutaneous nodules it was probably not an example of true exfoliative erythroderma Rodler-Zipkin (569) reported a 41 year old woman who had a generalized, diffuse reddening, scaling and thickening of the skin which was dry and "parchment like" She had lymphadenopathy and hepatosplenomegaly A 63 year old man, described by Ketron and Gay (338a), had generalized reddening and thickening of the skin as well as marked scaling and "warty" lesions around the ankles Arndt (14a) reported a 55 year old man who had a diffuse generalized erythema and lichenification of the skin, as well as superficial lymphadenopathy Linser's (394) patient was a 58 year old man who had generalized erythema and lichenification of the skin The cutaneous surface was covered with scales and the buttocks were excoriated There was enlargement of the spleen, liver and lymph nodes A 34 year old woman reported by de Graciansky *et al* (144), had a generalized desquamative erythroderma and lymphadenopathy of two years' duration The hemogram and cutaneous histologic picture revealed lymphocytic leukemia five years later She had temporary improvement following urethane therapy Degos *et al* (143a) reported a 57 year old man who a pruriginous, dry, exfoliating erythroderma which first appeared on the volar aspect of the left hand These lesions soon became generalized and pruriginous until the entire cutaneous surface was covered by smooth, noneczematous lesions of a uniformly red color There was slight diffuse infiltration on palpation of the lesions and moderate generalized lymphadenopathy The hemogram revealed 80 per cent hemoglobin, 4,200,000 red blood cells and 22,000 white blood cells per cu mm, with 44 per cent polymorphonuclears, 45 per cent lymphocytes, 10 per cent monocytes and 1 per

few months to several years are usually present for two years before death Autopsy usually discloses lymphocytic infiltration of the internal organs, as well as other characteristic findings present in lymphocytic leukemia

Histologic examination of these lesions reveals a dense uniform infiltrating band of lymphocytes, similar to the histologic architecture present in lichen planus There may be a very dense accumulation of miliary nodules in the upper and middle layers of the cutis which is determined by the manner of the development of this diffuse cutaneous disease, according to Gans (210a) The infiltration is formed by small deeply stained round cells which are morphologically identical to lymphocytes and larger elements having pale, oval nuclei which are interpreted as proliferative connective tissue cells The collection of cells adheres closely to the markedly dilated upper vascular net in the cutis although the papillary vessels are entirely free The infiltration appears to be separated from the epidermis by a uniform band of normal connective tissue The connective tissue cells are diffusely distributed but lymphocytes surround the hair follicles and sweat and sebaceous glands There may be "mast cells as well as numerous pigment cells" according to Arndt (14b) Numerous mitotic figures are present when the dermatitis is generalized

Localized Erythroderma The patient reported by Nomland (482) was a 64 year old man who had generalized pruritus for nine months before he presented cutaneous erythema followed by dark brown pigmentation Histologic study of the skin showed a "nonspecific picture" Ludy's (405) patient, a 39 year old Negro had generalized pruritus for one year, associated with localized erythroderma The cutaneous infiltrations varied from 2 5 to 10 cms in diameter One of the patients reported by Gate and Cullerct (213a case 1) had large cutaneous areas of erythroderma which were markedly pruritic

Granulocytic Leukemia There appears to be only one recorded case of generalized exfoliative erythroderma associated with granulocytic leukemia, that reported by Nekam, Jr

cent eosinophils The sternal bone marrow showed 22 per cent lymphocytes and 12 per cent monocytes The adenogram showed 32 per cent lymphoblasts, 20 per cent prolympho cytes, 23 per cent lymphocytes and 25 per cent multinucleated reticulum cells Histologic study of the skin indicated lymph ocytic leukemia His general condition and the hematologic picture improved following superficial roentgenotherapy, intramuscular injections of cortisone (200 mg) and vitamin B-12, but the cutaneous lesions persisted

Sequeira and Panton (625) described patients having "lymphoblastic erythroderma" which they first believed to be distinct from leukemic erythroderma These patients had from 8,000 to 30,000 white blood cells per cu mm, with 76 per cent lymphocytes, in some cases These cases are now believed to be characteristic of 'aleukemic" leukemia One of these patients, who was reported to have a normal peripheral white blood cell count, later presented the typical blood picture of leukemia, according to Dowling (151) Other cases of generalized exfoliative scaling erythroderma have been described by Hazen (269), MacLeod and Wigley (419b), Nicolau (479a), Scheer (602), Wechselmann (714), Wise (738), Wile (731b), Zumbusch (758) and Ormsby (494b, d)

There are also reports of exfoliative erythroderma associ ated with leukemia by Boardman (57), Cornell (124), N Epstein (167), Fox (194), Gattwinkel (215), Keim (333c), MacCormac (414a, b), Margarot *et al* (428), Neumark (476), Nomland (482), Oliver and Gold (489), Robert (565), Rusche (590), Schmidt (608), Snider (643), Werther (722a), Yamazaki and Nakano (747), and others

It is not possible to differentiate 'aleukemic" or lymphatic erythroderma from chronic universal exfoliative erythema due to other lymphomatous diseases by either clinical or histologic examination of the skin The diagnosis is dependent upon the finding of the leukemic architecture in the lymph nodes or bone marrow, since the peripheral blood picture may be normal These cutaneous lesions, which may be present from a

few months to several years are usually present for two years before death Autopsy usually discloses lymphocytic infiltration of the internal organs as well as other characteristic findings present in lymphocytic leukemia

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(472b) The patient with erythroderma described by Rodler Zipkin (569) had lymphocytic not granulocytic, leukemia Kueny and Petrovitch (358) reported a 38 year old man who had granulocytic leukemia for 18 months Exfoliative dermatitis which developed three weeks after deep roentgenotherapy was administered to the splenic area was believed to be due to the irradiation Although Burckhardt s (85) patient was thought to have typical granulocytic erythroderma Barney (28b) was of the opinion that this case suggested a chronic seborrheic eczema with secondary pyoderma resulting from therapy

Monocytic Leukemia The distinction between the so called Naegeli type of monocytic leukemia (which may be regarded as a variant of granulocytic leukemia with a predominance of monocytes) and the true Schilling type (monocytic leukemic reticuloendotheliosis) in which the cells are derived from the reticuloendothelial cells was stressed by Montgomery and Watkins (459e) Either type of monocytic leukemia has a primary autochthono is cutaneous origin

Montgomery and Watkins (459e) found that purpuric hemorrhagic or bullous cutaneous lesions frequently occur in the early stages of monocytic leukemia This is contrary to the usual occurrence of these lesions in the terminal stages of other lymphomatous diseases These lesions may result from specific infiltrations Bleeding of the gums and ulcerative gingivitis usually considered to be frequent manifestations of monocytic leukemia were not associated with exfoliative dermatitis in the patients described by Montgomery and Watkins Ulcers and furuncle like lesions usually occur as a late or terminal manifestation of monocytic leukemia Indurated eczematoid cutaneous plaques similar to those present in the early stages of mycosis fungoides as an initial manifestation of the disease was first noted by Loveman (398)

Another condition has been described which may present all the clinical features of mycosis fungoides but is identified histologically with leukemic reticuloendotheliosis although there is no hematologic evidence of leukemia Such cases

were reported as "aleukemic reticulosis"

According to Jaffe (314f), these cases are described as "reticuloendotheliosis" "reticulosis" "aleukemic reticuloendotheliosis" or "systemic hyperplasia of the endothelial cells of the blood forming organs" He stated that "the linking bridge among this group of diseases is more or less systemic hyperplasia without apparent cause either of the reticuloendothelial cells or of the reticular cells alone or of the endothelial cells Because the reticuloendotheliosis has often been associated with the formation of monocytes and because cases have been observed with an excessive amount of mononuclear cells in the peripheral blood some investigators have compared the hyperplasias of the reticuloendothelium with the systemic hyperplasias of the lymphopoietic and myelopoietic tissues and distinguish between them as aleukemic and leukemic reticuloendotheliosis Leukemic reticuloendotheliosis then would be identical with monocytic leukemia In reticuloendotheliosis it is not the character of the infection which leads to the peculiar histological manifestations but an abnormal irritability of the reticuloendothelium which may be acquired or congenital Acute leukemia is probably related to infections but the extensive proliferation of the immature myeloid or lymphoid cells overshadows the infection and the patients succumb to the disarrangement of the blood formation In reticuloendotheliosis the infection persists and the patient dies of the infection

"Aleukemic reticulosis has many features in common with Hodgkin's disease according to Dameshek (139b) He listed these features as (1) tendency to bouts of fever with typical Pel Ebstein relapsing fever (2) generalized lymphadenopathy and splenomegaly (3) presence of the type cell which is evidently the histiocyte and which frequently shows phagocytic qualities (4) tendency to form giant cells and (5) tendency to lay down large amounts of reticulum

Among the reported examples of this type Sezary (626a) in 1938 described what he considered to be a new form of malignant reticulosis The essential features consisted of

(472b) The patient with erythroderma described by Bodler Zipkin (569) had lymphocytic not granulocytic leukemia Kueny and Petrovitch (358) reported a 38 year old man who had granulocytic leukemia for 18 months Exfoliative dermatitis which developed three weeks after deep roentgenotherapy was administered to the splenic area was believed to be due to the irradiation Although Burckhardt's (85) patient was thought to have typical granulocytic erythroderma Barney (28b) was of the opinion that this case suggested a chronic seborrheic eczema with secondary pyoderma resulting from therapy

Monocytic Leukemia The distinction between the so called Naegeli type of monocytic leukemia (which may be regarded as a variant of granulocytic leukemia with a predominance of monocytes) and the true *Schilling type (monocytic leukemic reticuloendotheliosis) in which the cells are derived from the* reticuloendothelial cells was stressed by Montgomery and Watkins (459e) Either type of monocytic leukemia has a primary autochthonous cutaneous origin

Montgomery and Watkins (459e) found that purpuric hemorrhagic or bullous cutaneous lesions frequently occur in the early stages of monocytic leukemia This is contrary to the usual occurrence of these lesions in the terminal stages of other lymphomatous diseases These lesions may result from specific infiltrations Bleeding of the gums and ulcerative gingivitis usually considered to be frequent manifestations of monocytic leukemia were not associated with exfoliative dermatitis in the patients described by Montgomery and Watkins Ulcers and furuncle like lesions usually occur as a late or terminal manifestation of monocytic leukemia Indurated eczematoid cutaneous plaques similar to those present in the early stages of mycosis fungoides as an initial manifestation of the disease was first noted by Loveman (398)

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cific or nonspecific cutaneous manifestations, particularly exfoliative dermatitis, were frequent in monocytic leukemia (Schilling), since they may occur in 50 per cent of the cases (F W Lynch 409a) They described four patients in whom the cutaneous lesions appeared following the changes in the peripheral blood The first patient, a 76 year old man with exfoliative dermatitis, had previously been found to have lymphocytic leukemia when the hemogram was reported to show 21 850 white blood cells per cu mm with 75 per cent lymphocytes He had received superficial roentgenotherapy and "various types" of topical medications On examination he presented a generalized exfoliative dermatitis as well as diffuse cutaneous infiltrations, including small nodules on the legs and areas of lichenification There were hemorrhagic bullae on the hands and feet, impetiginous lesions around the mouth and nose and the skin showed a marked, diffuse brownish pigmentation The hemogram disclosed 14 2 gm hemoglobin 3 140 000 red blood cells and 67,400 white blood cells per cu mm, with 80 per cent of these cells of reticuloendothelial origin These findings definitely established the diagnosis of monocytic leukemia (Schilling) Histologic study of a cutaneous lesion revealed numerous monocytes with typical grooving of many nuclei a picture which is considered to be typical of this type of leukemia Similar findings were *present in* subsequent histologic studies of a lesion removed from another area of the body Repeated white blood counts ranged from 16 000 to 67,700 cells per cu mm and the proportion of reticuloendothelial cells reached as high as 90 *per cent* Their second patient a 20 year old man had a general[illegible]

[illegible] was given two treatments" with roentgen rays However, the condition was believed to be an atopic eczema "because *of his age*" On examination, the liver was slightly enlarged and tender Laboratory studies revealed the urinalysis to show a grade two albuminuria and, on microscopic examination, a few red blood cells The *hemo-*

large histiocytes which entered the blood stream and caused a leukemic condition This also produced the clinical picture of an intensely pruriginous edematous pigmented erythroderma Death occurred within 18 to 40 months Sezary was not able to classify these cells other than to designate them as monocytoid In our opinion these cases are similar to those of exfoliative dermatitis associated with monocytic leukemia as described by Montgomery and Watkins (459d)

On histologic examination of the cutaneous lesions Montgomery and Watkins (459e) found the changes to be specific for the Schilling type of monocytic leukemia in four of their patients who had exfoliative dermatitis and they were suggestive in the other cases In two cases touch smears of cutaneous lesions which had been excised for histologic study showed a picture identical to that of the peripheral blood smears The initial lesions in this type of leukemia may have a histopathologic picture identical to that of mycosis fungoides They believed that this finding is not surprising since involvement of the reticuloendothelial system of the skin as well as an increase in lattice fibers (gitterfasern) occurs in both conditions An infiltration which ranged from diffuse to densely nodular was sometimes limited to the upper portion of the cutis but often extended to the subcutaneous tissue As in mycosis fungoides the epidermis may be involved in the process or a "grenz or border zone may separate the epidermis from the infiltrate This infiltrate is most pronounced around the smaller blood vessels which show proliferation of the endothelium and adventitia and is composed chiefly of monocytic cells of varying degrees of maturity Although the nuclei are idented notched and kidney shaped the diagnosis is dependent upon the presence of numerous monocytes having longitudinal grooving of the nucleus according to Giffin and Watkins (224) Even though this longitudinal grooving results from the arrangement of the chromatin it appears to be a hyperchromatic longitudinal groove of the nucleus on microscopic examination

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gram showed 8 4 gm hemoglobin, 3,150,000 red blood cells and 16,800 white blood cells per cu mm, with 8 per cent lymphocytes, 5 5 per cent monocytes, 32 per cent segmented cells and 54 5 per cent eosinophils The high eosinophilia, together with the monocytes which contained nuclei, suggested a disease process involving the reticuloendothelial system

A 49 year old woman, reported by F T. Becker (37a), first presented a pruritic, papular cutaneous eruption which increased progressively to become nearly generalized Preceding menstruation, her skin became erythematous, the edema and pruritus increased markedly, and within 24 hours the skin would exfoliate in "large sheets" This exfoliation continued for three or four days after which the edema would subside leaving nearly generalized patches of "orange red dermatitis" Montgomery (459a) believed this case to "fit in well with" the previously described cases of exfoliative dermatitis associated with monocytic leukemia (Schilling)

O'Leary *et al* (488b) presented a 52 year old man who first had an erythematous papular cutaneous eruption involving the inguinal regions six years previously The eruption had gradually become generalized and was accompanied by severe pruritus, while circinate lesions and scattered "rough" plaques had occasionally appeared on the lower part of the abdomen during the preceding "several years" The face, neck, palms and soles had been involved for a period of three years and the pruritus was aggravated by heat and moisture He had received high and low voltage roentgenotherapy two and three years, respectively, prior to examination He presented a universal exfoliative dermatitis with purpuric lesions involving the face, abdomen, extremities and upper portion of the trunk, as well as generalized lymphadenopathy Examination of the sternal bone marrow disclosed occasional leukemic reticuloendothelial cells The hemogram revealed the hemoglobin and red blood cells to be "essentially normal" Four white blood counts showed 17,000, 44,300, 82,000 and 19,000 cells per cu mm and there were 44,000 thrombocytes per cu mm at one examination The differen-

tial ratio of leukocytes to leukemic reticuloendothelial cells was 41 per cent at one examination and 24 per cent at another

The patient described by Lamb and Stout (366) was a 72 year old man whose skin was dry and scaling He had numerous excoriated papules, which simulated prurigo (Hebra), distributed over the hands and arms while "pea to dime" sized pigmented red macules were present on the palms Larger, more numerous violaceous purpuric macules appeared on the face and within three weeks' time, spread to involve the neck and vesiculobullous lesions developed on the arms and hands A diffuse exfoliative erythroderma with a "peculiar hyperpigmentation" then gradually appeared Histologic examination of a cutaneous lesion showed monocytic leukemia of the Schilling type (leukemic reticuloendotheliosis)

Wayson and Weidman (712) reported their case as one of "aleukemic reticulosis" because leukocytosis did not occur at any time during the course of the disease This patient, a 36 year old man first noted an area of pruritic dermatitis above the interscapular areas which became generalized within the period of a few days The face, ears and interscapular, antecubital and popliteal regions were primarily involved by the dermatitis while the palms and soles were not affected These large, slightly infiltrated, furfuraceous and crusted erythematous plaques were intensely pruritic and following cleansing left a "raw red, weeping surface" He improved with "soothing" therapy but nine months later there was a mild recurrence accompanied by pruritus Two months later the character of the eruption had changed At this time there was involvement of both cheeks, the anterior portion of the chest, the extensor surfaces of both arms and inner aspects of the thighs with nonpruritic, discrete, irregularly shaped, reddish brown "patches" The distribution of the subcutaneous swellings was similar to the preceding diffuse cutaneous eruption in that the ears, cheeks, center of the forehead, tip of the nose, extensor surfaces of the arms, upper parts of the chest, both anteriorly and posteriorly, and the inner aspects of the

legs and thighs were involved These lesions varied in size and one on the right cheek was "as large as a pigeon egg" This patient died following "a slight pulmonary hemorrhage" 15 months after onset of the disease and nine weeks after the development of tumors A summary of the histologic observations revealed that the most massive involvement occurred in the skin lymph nodes spleen and bone marrow These changes which occurred in the same degree in all these organs *consisted of such extensive infiltration of monocytes and stellate and spindle cells* that the normal architecture was greatly destroyed Wayson and Weidman believed the affinities of such cells were established with the reticuloendothelial system because (1) blood forming tissues were the ones outstandingly affected and (2) the cell types concerned could be referred to that system by appropriate staining methods The latter phenomena observed in the liver and spleen established relationships between fixed cells of the reticuloendothelium and the free cells in the sinuses

Diagnosis

The diagnosis is established by a positive finding in any of the three following procedures (1) The histologic picture of the skin reveals a definite band like infiltrate of lymphocytes and lymphoblasts in the subpapillary layer of the corium associated with epidermal atrophy in devfoliation (2) histologic study discloses leukemic foci in the enlarged superficial lymph nodes which may be present for a period of "years" prior to positive cutaneous histologic or peripheral blood pictures and (3) the blood findings the white blood cell changes are least likely to be specific in leukemia and the total leucocytes and differential count may be normal for many years

Differential Diagnosis The following diseases may give rise to exfoliative dermatitis and should be considered in the differential diagnosis

A Secondary to Common Dermatoses
 1 Psoriasis

2 Seborrheic dermatitis
3 Various types of eczema, including atopic dermatitis
4 Lichen planus
5 Pemphigus foliaceus
6 Pityriasis rubra pilaris
7 Pityriasis rosea
8 Icthyosiform erythroderma

B Secondary to Systemic Diseases
1 Sarcoidosis
2 Internal malignancy

C Dermatitis Medicamentosa
1 Drugs, such as arsenic, "sulfas," quinine, penicillin, diethylstilbesterol, gold, codeine, barbiturates, atabrine, bismuth mercury, dinitrophenol thiocyanates, streptomycin, antitoxins, antipyrine, nearly any of the coal tar derivatives and quinidine

D Dermatitis Venenata (Contact Dermatitis)
1 Mercury, chrysarobin, penicillin or any drug which may cause a contact dermatitis It may extend and develop into exfoliative dermatitis

Complications

The complications of exfoliative dermatitis may be mild or severe The most frequent cutaneous complication is secondary pyogenic infection Although this infection is usually localized to the skin, it may invade the lymphatic vessels and produce lymphangitis and lymphadenitis or may result in septicemia, pyemia and metastatic abscesses by invasion of the blood stream

Pneumonia is the most frequent systemic complication and hypoproteinemia often occurs Hepatitis and nephritis may be toxic reactions Patients who have a long protracted exfoliative dermatitis show a higher incidence of tuberculosis than is evidenced in normal persons

Death may be due to the underlying disease, as in lymphomatous diseases, to intercurrent infections, such as pneumonia or to inanition and exhaustion

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A Secondary to Common Dermatoses
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Figures 98 and 99 Erythema multiforme following roentgenotherapy in a patient with lymphocytic leukemia

roentgen rays are infrequent When these lesions do occur the symptoms associated with mild forms may include fever tachycardia headache prostration asthenia and pruritus while pain in the back and joints nausea and vomiting may occur in patients having severe involvement Eosinophilia and leukopenia are present in the peripheral blood and urine examination shows albuminuria They described a 50 year old man with lymphocytic leukemia who had generalized intensely pruritic vesicular cutaneous lesions soon after intensive roentgenotherapy (6 000 r and 5 000 r respectively) The eruption regressed after cessation of treatment but reappeared when roentgenotherapy was resumed

Lortat Jacob *et al* (396) described bullous cutaneous lesions in a patient whose hemogram sternal bone marrow studies and lymph node histologic picture were all typical of leukemia The histologic examination disclosed dense compact clearly circumscribed leukemic infiltration surrounding the capillaries Rille's (564) patient with lymphocytic leukemia had cutaneous lesions which simulated those of exudative

Treatment

The treatment of exfoliative dermatitis is at best difficult and often unsatisfactory, since any therapy must necessarily be directed toward the underlying cause of the cutaneous condition However therapy may offer palliative relief until the true diagnosis can be ascertained

The type of local therapy is dependent upon the acuteness or chronicity of the process as well as upon the amount of exudation present The treatment for acute exudative reactions must be soothing and mild such as colloid baths wet dressings and "soothing lotions For the subacute or chronic phase mild stimulating ointments may be applied but should be used with caution

Antihistaminic drugs may alleviate the pruritus At the present time corticosteroids appear to be the best form of symptomatic therapy

5 *Erythema Multiforme (Including* ***Bullous Lesions)*** There are few reports of bullous lesions associated with leukemia In the majority of cases pruritus was usually present E Epstein and MacEachern (166) reported six patients who had bullous lesions associated with lymphomatous diseases Among these patients three had Hodgkin s disease two had granulocytic leukemia and one had lymphosarcoma but none had lymphocytic leukemia A patient who had vesicular and bullous cutaneous lesions which resembled those of pemphigus in association with lymphocytic leukemia was described by O Sachs (592) He also cited five other cases of this association reported in the literature

Polymorphous cutaneous eruptions precipitated by high voltage roentgenotherapy are believed to occur in predisposed persons as a result of absorption of products of cellular degeneration probably proteins present in both the irradiated lesions and in healthy tissues According to Mazzini and Blasi (441) such cutaneous eruptions should not be considered to be allergic reactions from drugs administered either during or following roentgenotherapy They believed that generalized cutaneous eruptions which occur following high doses of



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erythema multiforme These lesions underwent the typical color changes, contained vesicles of "hazel nut" size and were present on the palms A patient described by Scutt (618) had chronic lymphocytic leukemia associated with bullous cutaneous lesions on the palms and soles and a bluish infiltrated eruption on the face There were also four other types of cutaneous manifestations purpura, erythema multiforme-like lesions, cellulitis and specific papular infiltrates which were presumably a manifestation of erythema multiforme since a livid purplish erythema subsequently involved the entire face, except for the orbit There were ringed macules which resembled the "target" lesions of erythema multiforme on the trunk Traub (688b) reported a woman who presented cutaneous lesions as the initial symptom of lymphocytic leukemia She had "iris like' lesions, as well as bullae which resembled the lesions of dermatitis herpetiformis, involving the arms and hands

Gonin (235 case 1) reported a 58 year old man who had erythematous cutaneous plaques on both cheeks and an erythematous vesicular cutaneous eruption on the neck Milian (448) described a 47 year old woman who had a typical erythema multiforme five years previously Subsequently her general health declined and two years later she presented definite evidence of leukemia Other patients having vesicular or bullous cutaneous lesions have been reported by Ambrogio (6), Balassa (24), Bertaccini (44a), Goeckerman and Montgomery (229), Keim (333b), Kreibich (355b), Mariani (429), Milbradt (447), H E Miller (451), Oppenheim (492), Ormsby (494c), Parkes Weber (502c), Pollitzer (532) and S K Rosenthal (579)

The patient described by Hopkins (295) presented small, skin colored, firm, hyperkeratotic cutaneous lesions, characteristic of prurigo lymphatica, and bullous and erythematous lesions, as well as nodular infiltrations Specific cutaneous lesions associated with vesiculo-bullous lesions have been described by Chatellier and Sorel (111), Goldsmith (233b), Remenovsky (553) and M Wolf and Gounelle (742) The

51 year old man reported by Philadelphy and Halshofer (519) had chronic lymphocytic leukemia He presented a vesicular cutaneous eruption which was considered to be "gangrenous varicella." They cited another case, reported by Paltauf (499b) which they believed to be varicella associated with lymphocytic leukemia

Similar pemphigoid cutaneous eruptions associated with granulocytic leukemia have been described by Gelderman (218), Hudelo *et al* (299) Kuznitzky (361), Mayer (440) and Schulze and Schnitter (613b) Two of E Epstein and MacEachern s (166) patients had bullous cutaneous lesions associated with granulocytic leukemia

Bullous cutaneous lesions are rarely associated with monocytic leukemia However Osgood (496a) mentioned one patient who had a vesicular cutaneous eruption which simulated scabies and another patient who had cutaneous lesions which were thought to be erythema multiforme

6 Pyoderma The increased tendency toward the development of infection in all types of leukemia is well recognized since resistance to infections is very low when there is an



Figure 100 Pyoderma of the face associated with chronic lymphocytic leukemia (*A M A Arch Dermat 73 189 1956*)

Figure 101 Pyoderma of the scalp associated with chronic lymphocytic leukemia This lesion was originally believed to be the primary lesion of pemphigus

absence of normal defense cells The most frequent sites of involvement for infection appear to be around the teeth and gums and in the tonsils and rectum Infection occurs most often in acute leukemia, since leukopenia is frequent and the number of polymorphonuclears in the peripheral blood and tissues are reduced However, such infections may also occur in chronic leukemia when fever is usually present

Although cutaneous ulceration and abscess formation are a very frequent occurrence in acute leukemia, there are extremely few reports of this involvement of the anorectal region Five patients who had leukemia associated with anorectal lesions consisting of ulcers, abscesses, necrosis, and sloughing, were described by Blank (51) Two of these patients had acute "aleukemia," one lymphocytic, one granulocytic and one 'chronic' leukemia A patient with monocytic leukemia who *had necrosis in the anal canal was reported by Marks (431)* In the case described by Walsh and Sickley (705), the diagnosis of leukemia was made only after the anorectal lesions appeared Among 409 patients who had blood dyscrasias, reviewed by Birnbaum and Ahlquist (48), 14 (3 45 per cent) presented anorectal complications Two patients having acute leukemia and anorectal lesions which simulated lymphopathia venereum were described by Bluefarb (56e)

Histologic studies of the inflammatory reactions in 10 cases of leukemia were reported by Jaffe (314c) He stated "It has been shown that the type of response depends on the presence of myeloid tissue able to produce mature granulocytes In the presence of such tissue, the leukemic patient reacts to an infection like a normal person, while in the absence of such tissue the leukemic cells are not able to compensate, and the alternative changes predominate as they do in agranulocytosis and aplastic anemia It seems that for the leukemic organism von Mollendorff's conception of the myelopoietic potencies of the fibrocyte holds true The microscopic findings in inflamed tissue again demonstrate the sharp separation between lymphopoietic and the myelopoietic tissue Never was I able to find any indications of a transformation of leukemic

lymphatic cells into hemocytoblasts and granulocytes and whenever in lymphatic leukemia the body mobilized granulocytes it resorted to the undifferentiated germinal tissue about the blood vessels It is significant that in spite of the abundant proliferation of the lymphatic tissue the undifferentiated cells have retained their granulocytic properties As far as the inflammatory reactions are concerned there is no difference between the acute and the chronic leukemias which speaks against the conception held by Sternberg, and others that these two diseases do not belong together"

LYMPHOCYTIC LEUKEMIA Bousser *et al* (69a) described a 52 year old man with chronic lymphocytic leukemia who had a "giant" vaccinal pustule and secondary leukemic exacerbations 13 days after a smallpox vaccination Deviations in the peripheral blood picture were apparent 22 days after vaccination was performed They suggested that smallpox vaccination may be contraindicated in patients who have lymphocytic leukemia A patient with chronic lymphocytic leukemia reported by Greenaway (241) first presented cutaneous lesions which simulated those of chronic staphylococcic infection but the lesions later became eczematous and were associated with furunculosis

Jim and Reinhard (317) reported a 63 year old man who had agammaglobulinemia associated with chronic lymphocytic leukemia They found that marked diffuse destruction of the plasmacytes or reticuloendothelial cells replacement or infiltration by granulomata malignant lymphoma or leukemia may interfere with gamma globulin production resulting in agammaglobulinemia of the acquired type Lymphopenia and atrophy of lymphoid tissue appeared to be less severe in acquired than in congenital agammaglobulinemia Their patient died 10 months after onset of the disease and the histologic diagnoses at autopsy were chronic lymphocytic leukemia and disseminated cryptococcosis Among the many reports of agammaglobulinemia in the literature Jim and Reinhard were able to find reports of only two other cases in which the patient had chronic lymphocytic leukemia These patients had

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Histologic studies of the inflammatory reactions in 10 cases of leukemia were reported by Jaffe (314c) He stated "It has been shown that the type of response depends on the presence of myeloid tissue able to produce mature granulocytes In the presence of such tissue, the leukemic patient reacts to an infection like a normal person, while in the absence of such tissue the leukemic cells are not able to compensate, and the alternative changes predominate as they do in agranulocytosis and aplastic anemia It seems that for the leukemic organism von Mollendorff's conception of the myelopoietic potencies of the fibrocyte holds true The microscopic findings in inflamed tissue again demonstrate the sharp separation between lymphopoietic and the myelopoietic tissue Never was I able to find any indications of a transformation of leukemic

lymphatic cells into hemocytoblasts and granulocytes, and whenever in lymphatic leukemia the body mobilized granulocytes it resorted to the undifferentiated germinal tissue about the blood vessels It is significant that in spite of the abundant proliferation of the lymphatic tissue the undifferentiated cells have retained their granulocytic properties As far as the inflammatory reactions are concerned there is no difference between the acute and the chronic leukemias which speaks against the conception held by Sternberg and others, that these two diseases do not belong together"

Lymphocytic Leukemia Bousser *et al* (69a) described a 52 year old man with chronic lymphocytic leukemia who had a "giant" vaccinal pustule and secondary leukemic exacerbations 13 days after a smallpox vaccination Deviations in the peripheral blood picture were apparent 22 days after vaccination was performed They suggested that smallpox vaccination may be contraindicated in patients who have lymphocytic leukemia. A patient with chronic lymphocytic leukemia, reported by Greenaway (241), first presented cutaneous lesions which simulated those of chronic staphylococcic infection but the lesions later became eczematous and were associated with furunculosis

Jim and Reinhard (317) reported a 63 year old man who had agammaglobulinemia associated with chronic lymphocytic leukemia They found that marked diffuse destruction of the plasmacytes or reticuloendothelial cells replacement or infiltration by granulomata, malignant lymphoma or leukemia, may interfere with gamma globulin production resulting in agammaglobulinemia of the acquired type Lymphopenia and atrophy of lymphoid tissue appeared to be less severe in acquired than in congenital agammaglobulinemia Their patient died 10 months after onset of the disease and the histologic diagnoses at autopsy were chronic lymphocytic leukemia and disseminated cryptococcosis Among the many [illegible]

[illegible] leukemia These patients had

been described by Brem and Morton (75)

A patient reported by Vosbein (700) had impetigo contagiosum during the course of chronic lymphocytic leukemia. Hemorrhagic gangrene of the skin occurred in a patient with chronic leukemia described by Sarkany and Ransom (598). This 58 year old man first presented subarachnoid hemorrhage and moderate splenomegaly. The peripheral blood count showed 92 per cent hemoglobin and 12,900 white blood cells per cu mm, with 22 per cent polymorphonuclears, 0.5 per cent eosinophils, 1 per cent monocytes and 76.5 per cent lymphocytes, with no primitive forms. There were 168,750 blood platelets per cu mm and the bleeding and clotting times were normal. The bone marrow findings were typical of chronic lymphocytic leukemia. Three months later, fatigue and cough had developed and the sputum was tinged with blood. There were areas of cutaneous ecchymoses which progressed and became gangrenous. He died four months after the first symptoms had appeared and autopsy disclosed chronic lymphocytic leukemia and carcinoma of the lung. There was no evidence of primary growth in either the lungs or in any other organ. However, histologic study of the lung was "suggestive of primary carcinoma of the bronchus"

Levin (384b) reported a patient who had large cutaneous infiltrations on the back which were believed to be due to infection of the hair follicles. Machacek (415) reported a 66 year old man who had injured his thumb eight months previously. Three days later pruritic vesicles appeared at the site of injury and rapidly spread to involve both arms, the forearms and the face. On examination he had lymphangitis of the flexor surface of the right arm. A patient who had a succession of furuncles and abscesses on the upper portion of the body for "many months" before the diagnosis of lymphocytic leukemia was established, was described by Orhel (493)

Monocytic Leukemia. Staphylococcic infections, such as multiple furuncles and carbuncles, occur second in frequency to purpura in monocytic leukemia. The frequency of furunculosis in this type of leukemia appears to be more than merely

coincidental The cutaneous lesions may consist of all grades of suppuration from small pustules and furuncles to carbuncles These lesions may be generalized and when they involve the face may occur as impetigo or may simulate acne vulgaris on the face, neck and back The lesions may precede all other manifestations of leukemia for variable periods of time Resolution may occur, frequently leaving a residual brown pigmentation, indurated violaceous papules may appear around the primary lesion, or sloughing may result in indolent ulcers New groups of pustules may appear from time to time The necrotic ulcerative lesions were described by F W. Lynch (409a) as being tender to pressure but not markedly painful He found the lesions had a flat and necrotic base, sharp borders, and undermined edges Although the purulent discharge subsided within a few days, the lesions persisted unchanged for many weeks and there was little surrounding inflammation. Lesions which occurred early in the course of the disease sometimes healed without scarring but the lesions which appeared later showed no tendency toward granulation or epithelization Lynch reported that the histologic changes in the early stages of the disease consisted of inflammation associated with perivascular cellular infiltration, giant cells and necrosis In later stages of the disease, the tissue appeared to have lost its original "power to react," and he noted only a loose fibrillary granulation tissue One of Lynch's (409a case 8) patients was an 18 year old boy who first had a "blister' on the right calf which became dark in color and enlarged to 3 cms in diameter During the following week this lesion "dried" and central sloughing occurred Similar lesions, which showed all stages of evolution of the eruption, then developed on the left foot, hands, face and neck The ulcerated lesions, which were sharply marginated, had a firm base with central necrosis Another patient (409a case 7) presented inflammatory lesions on the face, neck and scrotum which became ulcerated and drained pus There were crusted, ecthymatous cutaneous lesions on the neck and cheek Another patient (409a case 5), with a generalized pustular cutaneous eruption, had an infec-

tion of the middle ear The lesions then became more severe and progressed to 0 5 cm, crusted, shallow ulcers The patient reported by Boles *et al* (62) presented a gluteal abscess and one patient described by Montgomery and Watkins (459d case 1) had impetiginized lesions around the mouth and nose

The occurrence of furuncles and carbuncles has often been reported One of Osgood's (496a case 3) patients first presented a furuncle on the chest and during the following two years numerous furuncles appeared on other parts of the body A large carbuncle appeared on the nape of his neck eight days before death Another patient (496a case 4) had furunculosis before the appearance of other symptoms of leukemia Orr (495a case 1) reported a patient who presented small painless cutaneous abscesses which progressed to form craters containing pus which, on culture, showed staphylococci A 44 year old man, who first had a furuncle on the abdomen three months previously, was reported by Hubler and Netherton (298 case 1) Similar lesions appeared on the trunk and lower extremities a short time later Herbut and Miller (277 case 6) reported a 57 year old man who had multiple furuncles on the face, neck and abdomen He died one year after the onset of furunculosis A 20 year old man who presented recurrent furunculosis, most marked on the shoulders and neck, seven months before the appearance of other symptoms of leukemia, was described by Fairburn and Burgen (175) Six months later furuncles again developed on the neck, shoulders and face followed, three months later, by cutaneous nodules on the right arm

Plum and Thomsen (529a) described two types of cutaneous lesions which occurred in three patients with monocytic leukemia They had (1) firm indolent cutaneous infiltrations which, on histologic examination, consisted of large accumulations of *monocyte* like cells and (2) *staphylococcic* infections, with pustules and furuncles The localized tumors composed of monocyte like cells, were found to be present in the skin, as well as in the ovaries and rectum Gregg (242), Labbe

et al (365a), Levy (387) and Luzina (408) have also reported cutaneous abscesses associated with monocytic leukemia

A patient reported by Marks (431) had involvement of the oral and anorectal regions associated with monocytic leukemia This 37 year old woman first presented a lesion which appeared to be an "aphthous ulcer," followed by a herpetiform lesion on the right shoulder two and one-half months later Weakness, fever, pallor, persistent fatigue, and moderate splenomegaly then occurred Five months after the initial le-

per cent lymphocytes and 4 per cent polymorphonuclears Two months later she had persistent pain in the rectal area, as well as erythema and swelling of the right upper quadrant of the perianal region Examination revealed "a ring of hypertrophied papillae partially covering a grey necrotic area involving a third of the mucocutaneous juncture" The trachea, vocal cords, and left tonsil became involved and a "necrotic membranous process" was apparent one month later There was some regression of these lesions following irradiation, but a temperature of 105 deg F then developed and remained septic throughout the course of the disease Numerous cervical lymph nodes became enlarged and there was marked swelling of the labia majora and perineum The entire circumference of the subcutaneous and superficial parts of the external sphincters were destroyed About six weeks before her death the hemogram revealed 30 per cent hemoglobin, 1,700 000 red blood cells and 13 850 white blood cells per cu mm, with 5 per cent polymorphonuclears and 95 per cent "atypical" monocytes She died nine months after the initial lesion had appeared in the mouth

Bonnin (64) believed that rectal lesions occur frequently enough to warrant repeated rectal examinations of these patients M J Lynch (410) and E White (727) also called attention to the ulceronecrotic lesions which involve the peri-

rectal region Among eight patients with monocytic leukemia reported by Sinn and Dick (633) five had perirectal lesions usually an anal fissure Two patients had asymptomatic anal fissures and one of these patients had a remission of the fissure following 6-mercaptopurine therapy but the lesion recurred five months later In two patients the perirectal abscesses were a severe complication of the disease When reviewing *the literature Sinn and Dick found that these patients evi*denced a marked lack of resistance to bacterial infections They frequently presented ulceration and infection of the oral cavity and perirectal regions as well as infected lesions in other parts of the body Furunculosis was frequent and bronchopneumonia occurred often particularly in the terminal stages of the disease

Bluefarb (56e) reported a 19 year old girl who first had an abscess of the left buttock near the rectum two months previously Subsequently intermittent fever and chills occurred She was known to have had monocytic leukemia for at least 18 months There was a granulomatous ulcer 10 by 5 cms in diameter which was clean and hemorrhagic but not painful involving the left buttock The rectal mucosa appeared very pale and amenorrhea had been present for the past two months The hemogram revealed 40 per cent hemoglobin 2 560 000 red blood cells and 6 500 white blood cells per cu mm with 69 per cent polymorphonuclears 3 per cent band cells 1 per cent eosinophils 1 per cent basophils 20 per cent lymphocytes and 6 per cent monocytes Anisocytosis polychromatophilia and hypochromia were all one plus The sternal bone marrow findings were compatible with those present in monocytic leukemia Histologic examination of a cutaneous lesion revealed granulomatous infiltration Biochemical examinations were reported to show 90 mg /100 cc non protein nitrogen 4 3 mg /100 cc creatinine and 1 77 gm /100 cc gamma globulin turbidity Treatment consisted of transfusions of whole blood and Erythromycin® The anorectal lesions improved with this therapy and she left the hospital two and one half months later Culture of the exu



Figure 102 Abscess of buttock associated with monocytic leukemia (case report) (*Quart Bull Northwestern Univ M School, 31* 198, 1957)

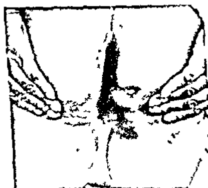


Figure 103 Rectal abscesses associated with granulocytic leukemia (*Quart Bull Northwestern Univ M School, 31* 198, 1957)

date from an abscess showed proteus vulgaris and beta hemolytic streptococci.

GRANULOCYTIC LEUKEMIA A 48 year old Negress, who had anorectal lesions which simulated lymphopathia venereum associated with granulocytic leukemia was reported by Bluefarb (56e) She had been in the hospital seven times during the preceding 14 months On the first examination, she had

"recurrent arthritis" with painful swelling of the ankles, knees and hands of two years duration, as well as rectal "soreness," pruritus and painful defecation of approximately the same duration Some of the recurrent rectal "boils" had required incision, while others had drained spontaneously She had severe, continuous pain of the neck and left ear, headache, nausea, vomiting and dysphagia of six weeks' duration She had received penicillin therapy both prior to, and following, the extraction of several teeth, but the headache and pains in the neck and ear persisted She also had recurrent epistaxis and alternating constipation and diarrhea Black stools and amenorrhea had been present for one month On examination she had edema of the ankles, exertional dyspnea and anorexia Her temperature was 102 1 F, there was pallor of the mucous membranes, moderate pharyngeal injection and both sterno cleidomastoid muscles showed spasm and tenderness The liver was palpable one fingerbreadth below the costal margin A "water pot' indurated perineum, with multiple perirectal and perineal sinuses drained a purulent exudate There were warm, tender swellings of the right hand, wrist, knee and ankle Laboratory studies revealed a positive blood serologic (Kahn) reaction Numerous bacteriologic cultures of the perineal pus disclosed hemolytic and nonhemolytic staphylococcus aureus, endameba coli, diphtheroids and pseudomonas Examination of the sternal bone marrow revealed increased cellularity, normal thrombocytic cells and normo blastic erythropoiesis The marrow was practically replaced by granulocytic cells with many blast forms and promyelo cytes, while very few mature granulocytic cells were present During two months in the hospital, the hemogram averaged 40 per cent hemoglobin 2 320 000 red blood cells and 3 500 white blood cells per cu mm, with 47 per cent polymorphonuclears, 4 per cent band cells 45 per cent lymphocytes and 4 per cent monocytes Toxicity, anisocytosis and occasional polychromatophilia' were observed

Biochemical studies revealed 3 2 gm /100 cc albumin, 4 0 gm /100 cc globulin, 2 57 gm /100 cc gamma globulin, 4 0

gm /100 cc. calcium organic phosphorus and 6 0 units (Mac-Lagen) th
tration of
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tered by transfusion, the anemia persisted She then noted tender bilateral swelling of the parotid glands, but this gradually subsided and the nausea and vomiting gradually ceased Three months after she entered the hospital the disease had become asymptomatic Five months later she presented generalized tender cutaneous nodules, marked swelling over the parotid and submandibular regions, intermittent epigastric pain, vomiting and exacerbation of the arthritis, but there was very little perirectal drainage On examination, she had small, tender subcutaneous nodules on the arms, legs and thorax There was tenderness in the region of the epigastrium, mild icterus of the sclerae, the conjunctivae were pale, and there were healed perineal sinuses The liver was enlarged 8 cms below the costal margin and the spleen was palpable. There were 0 5 cm lymph nodes in the inguinal and axillary regions and mild swelling and tenderness of the right knee, ulnar deviations of the hands and clubbing of the fingers

The sternal bone marrow showed moderate increased cellularity, normal thrombocytic cells, almost complete replacement by immature granulocytic cells, predominantly monoblastic, and increased numbers of plasmacytic, eosinophilic and reticulum cells The sedimentation rate was 15/mm per hour, the hematocrit 15 per cent There was herpetic stomatitis. The hemogram averaged 31 per cent hemoglobin, 1,407,000 red blood cells and 5,300 white blood cells per cu mm, with 20 per cent polymorphonuclears, 7 per cent band cells, 15 per cent lymphocytes, 6 per cent monocytes, 47 per cent myeloblasts, 2 per cent progranulocytes, 1 per cent metamyelocytes and 2 per cent myelocytes Rouleaux of the cells were noted Therapy consisted of 600,000 units of penicillin a day, 1,000 cc whole blood by transfusion, and sitz baths She had a low grade fever, up to 100 F, which gradually subsided, the subcutaneous nodules regressed completely, and her only com-

plaint was that of "weakness" Seven months later the vomiting and dull aching epigastric pain had recurred and hoarseness was apparent The spleen was palpable 4 cms below the costal margin and the perianal fistulae had again begun to drain

The sternal bone marrow showed marked cellularity and normal thrombocytic cells, but reduced erythropoiesis and granulopoiesis, with a shift to the left of the blast cells Pro granulocytes and granulocytic cells predominated and there were increased numbers of plasmacytes, reticulum cells and lymphocytes Further transfusions of whole blood were ad ministered, as well as potassium citrate, penicillin, streptomycin and oxytetracycline A month after admission to the hos pital, she had severe rectal bleeding and proctoscopic exami nation disclosed multiple abscesses with fistulous openings in all perianal quadrants, scarring, contracture and stenosis of the sphincter The bleeding then subsided and again her only symptom was "weakness" She was seen again 11 months after the onset of her illness, at which time she had epistaxis She was given short courses of sulfadiazine and Erythromycin®, as well as transfusions of whole blood (three liters) As previously, her only complaint was that of weakness Two months later she had an ulcer, which drained, on the buttock This was followed by increased weakness, vomiting, loss of weight and anorexia There were small, shotty, slightly tender lymph nodes in the cervical, axillary and epitrochlear regions, while the inguinal lymph nodes were large the spleen palpable 6 cms and the liver 10 cms, below their costal margins Rectal stricture was now present

She responded fairly well to treatment with transfusions of whole blood (1 5 liters), chlortetracycline and six mercapto purine However, two months later she had severe diarrhea, extreme weakness, dyspnea and numbness of the legs and left hand Her general condition continued to decline, the neck veins became distended, dyspnea increased and pulmonary rales were noted She died 15 months after the onset of ill ness At autopsy, histologic study of an ulcerated rectal lesion

revealed a dense infiltration of cellular elements at the base which extended deep into the wall of the rectum These cells consisted of histiocytes, megakaryocytes, and myeloblasts with myelocytes predominating There were few polymorphonuclears Regressive changes, consisting of fibrosis, were noted in a portion of the rectal wall There was also a leukemic infiltration with megakaryocytes in the kidneys, uterus, lymph nodes appendix bone marrow, liver, spleen and heart The histologic findings were those of subacute to chronic granulocytic leukemia The prominent infiltration of megakaryocytes in several organs was a somewhat unusual finding The histologic structure of the rectal lesion did not resemble that of lymphopathia venereum and this lesion was believed to be due to a nonspecific process with subsequent localization into the area of leukemic infiltration

Belding *et al* (41) pointed out that the development of infection in the Naegeli and Schilling types of leukemia was not closely related to granulocytopenia Among eight patients having monocytic leukemia (Naegeli type), none had granulocytopenia during the course of their infection while four patients with histiocytic (Schilling type) leukemia had granulocytopenia without intercurrent infection Infections of the oral cavity with ulceration and necrosis of clinical significance occurred in four patients with the Naegeli type but in none of those with the Schilling type However, slight ulceration of the oral cavity occurred in two patients with monocytic leukemia and in two with histiocytic leukemia Of the two with histiocytic leukemia one had leukemic infiltration of the tonsils with slight pharyngeal ulceration and the other had granulocytopenia with only terminal and minor ulceration of the gums and tonsils In this particular series of cases, the development of lesions in the oral cavity was not associated with granulocytopenia The eight patients who had a significant degree of oral involvement were evenly divided as to the presence or absence of granulocytopenia

Case Report A 50 year old man had weakness, severe sweating loss of appetite lymphadenopathy and

loss of weight for the preceding two months During the week after he entered the hospital partial deafness developed as well as cellulitis along the right side of the neck and face There was cervical axillary and in guinal lymphadenopathy and hepatosplenomegaly He had an ulcer on the lingual aspect of the lower gum Urine examinations disclosed albumin and granular casts The hemogram showed 60 per cent hemoglobin 3 050 000 red blood cells and 207 000 white blood cells per cu mm with 80 per cent lymphocytes 14 per cent disintegrated cells 3 per cent polymorphonuclears and 3 per cent lymphoblasts He died one month later and the autopsy diagnoses were chronic lymphocytic leu kemia with cervical axillary inguinal and mediastinal lymphadenopathy, as well as lobar pneumonia of the right upper lobe The skin showed pallor and super ficial ulcerations 2 cms in diameter which involved the lower right cervical region and were surrounded by pink discoloration with loose undermined edges con taining a small amount of seropurulent material Histo logic studies revealed lymphocytic leukemic infiltra tions of the liver kidneys lymph nodes spleen and skin

Case Report A 37 year old man was found to have granulocytic leukemia seven months previously He had weakness for three years preceding this diagnosis At 11 years of age a thyroglossal cyst had been excised but had continued to drain a purulent exudate during the next 26 years He had occasional cough with ex pectoration mild shortness of breath and a large mass in the left upper portion of the abdomen Six months after the diagnosis of leukemia had been made furun cles appeared on various areas of the body He was given roentgenotherapy and the furuncles all regressed except for one on the right wrist However during the past month he had frequent chills followed by marked fever and there was some bleeding from the gums and occasional epistaxis On examination he

had lymphoid tissue in the right tonsillar fossae and an irregular scar with a sinus opening in the center of the anterior region of the neck with residuals of a thyroglossal cyst The spleen was palpable below the level of the umbilicus and the liver was palpable 8 cms below the costal margin The hemogram revealed moderate secondary anemia and chronic granulocytic leukemia During 41 days in the hospital, the hemogram averaged 66 per cent hemoglobin, 3,346,000 red blood cells and 143,700 white blood cells per cu mm, with 6 per cent metamyelocytes, 10 per cent band cells, 43 per cent polymorphonuclears, 4 5 per cent lymphocytes, 4 5 per cent eosinophils, 24 5 per cent segmented cells 6 5 per cent monocytes and 1 per cent basophils Histologic examination of a lesion revealed cutaneous infiltration with some round cells, others appeared to be young granulocytes There were a few mature poly-

ly of granulocytic leukemia, whereas it is frequently present in Hodgkin's disease When pruritus occurs with leukemia, it is usually accompanied by exfoliative dermatitis, urticaria, prurigo-like papules, eczematoid lesions, or jaundice However, pruritus may be present without nonspecific cutaneous lesions, as in the cases described by Wile (731c) Ludwig (404) and Webster *et al* (713a) Wile's patient had moderate pruritus of the extremities for three years and generalized pruritus, as well as copper brown cutaneous pigmentation, most marked on the trunk, associated with numerous fine telangiectases and marked scaling infiltration which had been present for seven months There was an extensive papillomatous tumor involving the wrists dorsal surfaces of the hands, feet and ankles

The patient reported by Levin (384c) had persistent generalized pruritus associated with numerous cutaneous excoriations and scattered wheals Levin (384b) also described a 58

year old man who had a generalized, markedly pruritic cutaneous eruption He had universal erythema and edema which was most marked on the face and hands

One of the patients reported by Gate and Cuilleret (213a case 2) had generalized pruritus associated with erythematous cutaneous lesions Gottron's (238b) patient, a 68 year old woman with leukemia, had papular urticarial lesions and pruritus A 54 year old woman, reported by Riecke (560), had urticaria and intense pruritus for four years Histologic study of the turbinate mucosa revealed diffuse lymphocytic infiltration along the walls of the blood vessels

There are a few reports of pruritus in association with lymphocytic leukemia Among these cases, Hartzell (262) reported a 45 year old man who had numerous markedly pruritic lesions on the buttocks, forearms, elbows, wrists, and posterior surface of the thighs These lesions were flat, wheal-like raised, and 1 5 by 1 5 cms in size One of the patients described by Ikegami *et al* (307 case 1) was a 34 year old man who had generalized markedly pruritic cutaneous erythema infiltration and fine scaling most marked on the face, neck and anterior portion of the chest Jakac's (315) 56 year old patient, who had chronic lymphocytic leukemia, presented *intensely pruritic generalized cutaneous lesions* which were eczematoid and urticarial

A 67 year old man who had generalized pruritic cutaneous lesions and necrosis of the upper lip, associated with subacute granulocytic leukemia was reported by Ikegami *et al* (307 - case 3)

Reich's (550) patient was a 37 year old man who presented generalized pruritus as one of the initial symptoms of chronic monocytic leukemia The man reported by Weissenbach *et al* (719b) had urticarial lesions and acute circumscribed, relapsing pruritic edema, associated with monocytic leukemia A patient described by Ikegama *et al* (307 case 2) was a 22 year old man who had purpura and diffuse cutaneous infiltration of the face, neck, breast and back, associated with monocytic leukemia Gessler's (222) patient, a 36 year old woman,

first presented a pruritic erythema on the inner aspects of both thighs followed one month later by a similar eruption on the neck and forearms Seven months after the appearance of the cutaneous lesions the diagnosis of monocytic leukemia was apparent

Erythema nodosum has been described in association with leukemia A patient who had these two conditions was re ported by Gate and Culleret (213a) Kourilsky *et al* (351) reported a 69 year old man with acute "aleukemic" leukemia who had erythema nodosum Piacentini (522) described a 33 year old woman with chronic granulocytic leukemia She had 130 000 peripheral white blood cells per cu mm and the spleen measured 28 cms Following the administration of Desacetylmethylcolchicine® for 45 days the white blood cells numbered 18 000 per cu mm and the spleen measured 20 cms However further treatment with this drug resulted in an increase in the number of peripheral white blood cells rheumatic symptoms and erythema nodosum These symptoms continued for four weeks at which time she was given Desacetylmethylcolchicine with 1 4 – Bismethylsul fonoxybutane® for a period of 20 days A total and prolonged remission then occurred the rheumatic and splenic symptoms disappeared and the hemogram became normal The patient reported by Wintrobe and Mitchell (737c) also had erythema nodosum associated with granulocytic leukemia One of the patients described by F W Lynch (409a) had erythema nodosum and monocytic leukemia

Erythematous lesions are sometimes present with leukemia Cordiviola (122) reported a 68 year old woman with lympho cytic leukemia who had an erythematous and edematous ery sipeloid cutaneous eruption on the left hand following the administration of urethane (72 gm) She had repeated exa cerbations of this eruption and Loeffler s syndrome of the lungs with eosinophilia and cutaneous eosinophilia occurred Gonin (235) reported two patients who had lymphocytic leu kemia associated with erythematous cutaneous lesions A 48 year old woman described by G S Smith (640b) had an

erythematous cutaneous eruption on the trunk associated with chronic monocytic leukemia

Urticaria may occur as a nonspecific cutaneous manifestation of lymphocytic leukemia or it may occur in association with leukemic cutaneous nodules When persistent urticaria has been present for a long period of time, the diagnosis of leukemia should be considered and sternal bone marrow examinations, as well as repeated hemograms should be done Grosglik's (245b) patient with granulocytic leukemia presented urticarial lesions, which resembled angioneurotic edema, following roentgenotherapy However, a patient reported by Levin (384a) had urticarial lesions which regressed, leaving pigmentation, following roentgenotherapy A 32 year old man, reported by Poche and Stuttgen (530) had chronic urticaria 16 months before his death and reticuloendothelial infiltrations characteristic of monocytic leukemia were present

Edema has been reported in association with leukemia Paviot *et al* (510) described a 78 year old man who had edema of the lower extremities and red, mottled cutaneous lesions on the left thigh of six weeks' duration A 29 year old woman with chronic granulocytic leukemia who had transient edema of the extremities, which lasted for two to four days, was reported by Jurgens and Kaether (323)

A patient with "aleukemic' granulocytic leukemia who first had eczematoid cutaneous lesions on the right leg eight years previously, followed by specific nodular cutaneous lesions, was described by Morrissey (463) Burckhardt's (85) patient, a 37 year old man, had granulocytic leukemia associated with a markedly infiltrated, generalized cutaneous eruption which resembled seborrheic dermatitis Scholtz (609) reported a 64 year old man who had granulocytic leukemia and "weeping" crusted cutaneous lesions on the nose, left axilla and anterior portion of the trunk The cutaneous lesions simulated those of infectious eczematoid dermatitis

Mimuro's (453) patient, a 49 year old man, presented numerous miliary exanthems of the left leg during the early

stages of leukemia The patient reported by S W. Becker (38) had urticaria and specific cutaneous nodules associated with leukemia Pautrier's (509b) patient had cutaneous lesions which simulated erysipelas during an acute phase in the terminal stage of leukemia

8 *Pigmentation* Pigmentation is not frequently associated with chronic leukemia E Epstein and MacEachern (166) found pigmentation to be present in two of 90 cases of granulocytic leukemia, in one of 60 cases of lymphocytic leukemia, and in none of the 10 patients having monocytic leukemia

According to Jaffe (314a), the cutaneous pigmentation is greyish brown in color, resembling that of Bantis disease, in chronic granulocytic leukemia but a hemorrhagic diathesis may occur in acute granulocytic leukemia

Since large doses of arsenic (Fowler's solution) may be administered for prolonged periods of time to patients with chronic granulocytic leukemia, Sturgis (662a) believed that some cutaneous pigmentation might result from this therapy Arsenotherapy may cause cutaneous changes such as diffuse erythema diffuse brownish red pigmentation or, rarely, melanoderma although the most characteristic lesions are the so-called "rain drop" pigmentation and keratoses of the palms and soles One of Hazen's (269 case 1) patients was a 60 year old man who presented cutaneous pigmentation prior to arsenotherapy for chronic lymphocytic leukemia The bronze color of the skin simulated arsenical pigmentation and there was also a "slight greenish cast" to the skin This pigmentation was of a uniform distribution and the margins gradually merged into the surrounding skin with no definite border

Kwiatkowski (364) reported a 56 year old woman who had cutaneous hyperpigmentation and depigmentation, as well as cutaneous atrophy of the left arm

Melanuria without melanotic growth, in association with leukemia was reported by Bonnet (63) It was suggested by Rolleston (572a) that leukemic infiltration of the liver might result in hepatic insufficiency Haden and Orr (249c) believed that the action of tyrosinase on the oxyphenyl deriva-

tives of the increased proteolysis produced in leukemia resulted in pigmentation

JAUNDICE Jaundice, when associated with leukemia, is usually *due to leukemic infiltration of the liver* Severe jaundice, resulting from obstruction of the common bile duct by enlarged portal lymph nodes, rarely occurs in leukemia However, such a case was described by Bower and Coca Mir (70) This patient had a normal peripheral white blood cell count on admission to the hospital but leukopenia then occurred and a superior vena cava syndrome developed There was marked dilatation of the common bile duct by enlarged portal lymph nodes

Jaundice is apparently extremely rare in association with chronic granulocytic leukemia The patient reported by Tixier and Troisier (286) had hemolytic jaundice and granulocytic leukemia



Figure 104 Alopecia associated with chronic lymphocytic leukemia (*A M A Arch Dermat*, 73 189, 1956)

A 55 year old woman described by Marchal *et al* (426), had icterus of the skin and sclerae, as well as intermittent jaundice, for a period of four months Autopsy disclosed lymphocytic leukemic infiltration of the spleen, liver, kidneys lungs and heart

9 *Trophic Cutaneous Changes* Trophic changes, associated with leukemia usually occur with exfoliative dermatitis Patients who had trophic changes of the nails, skin, and hair are described under Exfoliative Dermatitis (Section 4)

The patient reported by Calvert and Smith (93) was a 70 year old man with lymphocytic leukemia who had metastatic acropachy He had leukemic infiltration of the hands with the "hybrid" appearance of multiple enchondromatosis and tetralogy of Fallot and "horn like nails as well as rhinophyma There was inguinal axillary and cervical lymphadenopathy Following urethane therapy (1 gm daily for 14 days), the peripheral blood picture became "more normal" but the acral lesions did not improve His general health remained good during the following 11 months but the acropachy became more marked

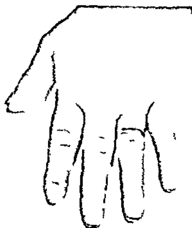


Figure 105 Trophic changes of the nails associated with chronic lymphocytic leukemia

Garvey and Lawrence (212) reported a 46 year old woman who had bilateral facial paralysis Autopsy examination disclosed leukemic infiltration of the seventh cranial nerves and lymphocytic elements in the oculomotor nerves, but no involvement of the spinal cord Kwiatkowski's (364) patient, a 56 year old woman, had received roentgenotherapy for lymphocytic leukemia Six months later trophic changes occurred in the left arm, as well as atrophy of the muscles, ankylosis of the joints and rarefaction of the bones, probably from leukemic infiltration of the spinal nerve roots Histologic examination of the skin showed small nests of leukemic infiltration throughout the corium, each group being about 0 5 mm in diameter Histologic study of the "grossly normal" skin and areas in which vitiligo had occurred, also showed leukemic infiltration but of a lesser degree, the nests of leukemic infiltration were smaller and further apart It was believed that the trophic changes of the arm produced a *locus minoris resistentiae* which resulted in the greater growth of leukemic foci in these areas

A woman reported by Cumming (133) had complete denudation of the tongue associated with severe pain which caused difficulty in the ingestion of fluids There were numerous pruritic hyperkeratotic plaques on the body and those involving the palms soles and groins were tender on palpation Examination of the sternal bone marrow revealed granulocytic hyperplasia with involvement of the reticulum, which showed numerous mitotic figures There was also leukemic infiltration present at the base of the nails which is a very rare occurrence in leukemia Krabbe (352) described a 44 year old woman with chronic lymphocytic leukemia who had a contracture of the fingers, with limitation of motion and atrophy of the interossei muscles and thenar and hypothenar eminences This involvement was believed to be due to polyneuritis with trophic changes, also a rare finding in leukemia

Another rare type of cutaneous involvement was described by Legrand *et al* (377) This patient, a 54 year old woman, had cutaneous lesions as the only manifestation of lymphocytic

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T B Schwartz and Jager (616) reported a 43 year old man who had cryoglobulinemia and Raynaud s disease associated with chronic lymphocytic leukemia During the previous seven years he had noted stiffness cyanosis and pain in areas of the body exposed to cold as well as multiple infections and eczematoid cutaneous lesions on the extremities The hemo gram disclosed moderate normocytic anemia and lympho cytosis which was characteristic of chronic lymphocytic leu kemia Histologic studies showed leukemic infiltration of the skin He had moderate proteinuria and slight nitrogen re

She had a persistent fever and intermittent cutaneous lesions which were believed to be panniculitis of the Christian Weber type She was treated with roentgen rays urethane Dichloren® Teropterin® penicillin strepto mycin, Antistin® and Phenergan® Preceding death her tem perature was 104 to 105 F marked splenomegaly developed and there were numerous myeloblasts in the peripheral blood

The occurrence of venous spiders associated with chronic lymphocytic leukemia was reviewed by Juniper (322) He described a patient with cutaneous venous vascular forma tions resembling arterial "spiders" such as those usually as sociated with chronic liver disease However they were proved to be of venous origin and were believed to be asso

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ciated with the lymphocytic leukemia rather than as a result of involvement of the liver Bean (34) described the "venous star as a lesion which may resemble an arterial "spider" It appears as a blue or red circumscribed cutaneous lesion which results from dilated underlying veins due to venous obstruction associated with persistent elevation of venous pressure It usually occurs with superior vena cava obstruction and is usually present over large veins into which it drains Although the blood flow is toward the center the vessels fill by reflux from the center after pressure The venous star usually involves the lower portion of the ribs dorsum of the foot lower portion of the legs or ankle area or the medial aspect of the thighs However it has been described involving the back at the junction of the neck and thorax and the area above the sacrum These lesions usually occur after adolescence but have also been reported in young children Women appear to be more frequently affected than men Venous thrombi associated with metastatic leukemic infiltrations have been described Among these cases Madden (420a) reported a patient who had telangiectatic lesions associated with granulocytic leukemia However in none of the reported cases did the lesions resemble spiders" according to Jumper In his case the vascular formations were related to venous thrombosis Although the immediate cause was not apparent he believed it may have been related to the leukemic process There was not sufficient leukemic infiltration in the center of the lesions to indicate a direct causal relationship between the cutaneous lesions and the granulocytic leukemia

10 Other Cutaneous Reactions Various uncommon cutaneous manifestations are sometimes described in association with leukemia Bruwer *et al* (82) reported that cutis verticis gyrata may occur with leukemia Stewart s (653) patient had herpes simplex with herpetiform and ulcerated cutaneous lesions around the mouth The 42 year old man reported by Liebner (390) had aphthous lesions involving the mouth and tongue and herpes simplex of the nose chin ears and scrotum

Sheldon and Young (630) reported a 17 year old boy who had typical dermatomyositis associated with leukemia At autopsy, there was a "thick white infiltrate" in the mediastinum and yellowish nodules in the liver and spleen which showed, on histologic examination numerous large monocytes

It is known that patients who have chronic lymphocytic leukemia do not react favorably to smallpox vaccinations and such vaccinations should be performed only when absolutely necessary Beerman and McGuire's (40) patient a 33 year old woman had a severe reaction to smallpox vaccination The vaccination site became edematous ulcerated and inflamed She presented edematous cutaneous lesions which involved the nose and right infraorbital region, as well as a vesicular pustular cutaneous eruption on the hands wrists forearms face and scalp Zugerman (757) described a patient with chronic lymphocytic leukemia who had a generalized pustular eruption two months after vaccination and he subsequently died A patient with chronic lymphocytic leukemia who had



Figure 105A Gangrenous lesion following smallpox vaccination in a patient with chronic lymphocytic leukemia (Courtesy A Rostenberg M D and R S Medansky M D)

a generalized vaccinia following vaccination and subsequently died was described by Thomsen (681) Olansky *et al* (487) reported a 42 year old woman with chronic lymphocytic leukemia who had received cortisone therapy Herpes simplex then appeared on the lower lip and two smallpox vaccinations were given A generalized vaccinia occurred and she died 49 days after the first vaccination had been given They stated that the "introduction of live viruses into patients receiving cortisone may be unwise, and additional studies in this respect seem indicated"

Bakalos and Thaddea (23) reported a patient with monocytic leukemia who presented condyloma like proliferations in the anal region

One of F W Lynch's (409a case 2) patients, a 58 year old woman, had chronic granulocytic leukemia Numerous noninflammatory, infiltrated cutaneous lesions appeared on the arms, buttocks and on one area of the leg The latter lesions



Figure 106 Phlebitis in a patient with chronic lymphocytic leukemia (*A M A Arch Dermat*, 73 189 1956)

were believed to be "thrombophlebitis" Keim's (333c) patient had chronic lymphocytic leukemia associated with cutaneous lesions which resembled poikiloderma atrophicans vasculare Ramel (546) reported a patient with chronic granulocytic leukemia who had *cutaneous lesions of granuloma* annulare which regressed spontaneously

Dermatomyositis occurring in a 17 year old boy was reported by Sheldon and Young (630) At autopsy there were "dense" white infiltrations in the mediastinum and yellowish nodules in the liver which were found to consist of monocytes, on histologic examination The muscles, which were pale and edematous, were infiltrated with plasmacytes and histiocytes This was a more severe inflammatory picture than that present in the other organs Leukemia or lymphadenic dermatomyositis with reticulate poikiloderma was described by Gery *et al* (221)

PRIAPISM Priapism is another sign which had been reported to occur in association with chronic lymphocytic and granulocytic as well as in acute forms of leukemia It is frequently mentioned in textbooks as a complication of leukemia However, the impression that priapism is a frequent occurrence in leukemia appears to be erroneous Craver (130a) believed this association to be extremely rare, since he found only one case of priapism among 100 cases of leukemia This patient, a 24 year old man, had priapism for 19 days The hemogram revealed 179,000 white blood cells per cu mm and the typical findings of granulocytic leukemia He was given low voltage roentgenotherapy (100 r each treatment) over the spleen for five consecutive days On the fifth day the priapism and pain disappeared but impotence followed According to Craver, actual leukemic thrombi have been found in the corpora cavernosa in a few cases but no clot was found in other cases in which the corpora cavernosa was examined

There is a much higher incidence of priapism associated with acute or chronic leukemia reported in the older literature In 1914, Hinman (284) reported leukemic priapism in 25 per cent of the cases he studied Among the reported

cases Cattaneo (106) and Kaplan (327) found the incidence to be as high as 40 per cent However priapism as a complication of leukemia is reported only rarely in contemporary literature Lower and Christoferson (399) reported such a case and reviewed the literature They found an incidence of only 0 65 per cent among the reported cases

In a few cases priapism was the initial manifestation of leukemia as described by Achard (2) Conn (119) Macciotta (413) and Podkomorski (431) Priapism appears to occur more frequently with granulocytic leukemia than with other types of leukemia

Priapism occurring during the course of leukemia has also been described by Andersen and Nielsen (7) Bogaert (59) Dabove *et al* (137) Denechau (148) Lambin (367) J R Robertson and McDaniel (566) and Romano *et al* (573)

Kulka (358) reported a 72 year old woman who had priapism of the clitoris She had an ulcerated hard painless somewhat larger than a plum sized tumor which was somewhat fixed to the underlying tissues involving the region of the clitoris Kulka ascribed the initial swelling of the clitoris to a thrombus of the corpora cavernosum and the gradually enlarging tumor to extravasation of lymphocytes within the clitoris and their subsequent growth in that region

Among the histologic studies of leukemic thrombosis of the corpora cavernosum those described by Kast (331) in 1895 remain illustrative His patient who had leukemia for several months had priapism for six weeks before death At autopsy cross section of the penis showed that the structure of the corpus cavernosum penis was barely recognizable On histologic examination there was a dense connective tissue layer enclosing the cavernous bodies There were numerous polymorphonuclears intermingled with lymphocytes which filled the cavernous spaces but in the central portions these spaces were entirely absent and there were only tiny slit like" spaces which were filled with polymorphonuclears However the major central portion consisted of homogeneous connective tissue apparently the end product of leukemic thrombosis

VIII

PATHOLOGY OF CUTANEOUS LEUKEMIA

Lymphocytic Leukemia The histologic picture of the cutaneous nodules which occur in lymphocytic leukemia are usually pathognomonic of the disease The epidermis is separated from the tumor like infiltrate by a narrow zone of connective tissue The infiltration of the cutis consists almost



Figure 107 Normal zone of connective tissue separating the epidermis from the infiltrate

entirely of lymphocytic and lymphoblastic cells which end in a sharp line just beneath the papillary layer The individu



Figure 108 Infiltrate ending in a sharp line just beneath the papillary layer

al nodules may be composed of a solid mass of cells or may consist of numerous small nodules Strands of cells sometimes branch out into the surrounding tissue At the onset of the

Figure 109 Nodule consisting of a solid mass of leukemic cells

Figure 110 Large nodule composed of smaller nodules

disease, the cells appear to be definitely arranged about the hair follicles, sebaceous and sweat glands, and blood vessels and are separated by connective tissue This separation from

Figure 111 Strands of leukemic cells branching out into surrounding tissue (low power)

Figure 112 High power magnification of Figure 111

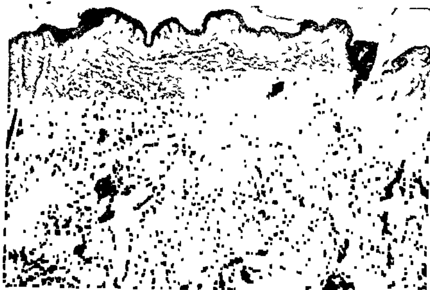
the papillary and subpapillary layer is evidenced by a small band of edematous connective tissue which is pierced by



F gı e 113 Periglandular nfiltrate

F gu e 114 Peri ascular and periglandular ınfiltrate

d lated vessels and lymph spaces The cells orıg nate and accumulate here from the deeper vascular net vork of the cutis and the cellular ınfiltration penetrates upward and down



the cutis

ward, but is grossly adherent to the vessels The infiltrating cells surround the vessels in a cylindriform or bandlike manner in the early stages of the disease when the uniformity of the cell types are characteristic However, all stages of development, including large, sharply defined, nodular masses of infiltration, may be present in lesions of long duration. In these lesions, the cell deposits in the connective tissue network are clearly recognizable and more uniform than in the early exfoliative type of lesion There may be plasmacytic cells at the border of the lesion, the connective tissue cells may be increased in number and few mitoses are present. The hair follicles, sebaceous, and sweat glands may be absent in the larger tumors, while in the smaller lesions the process appears to originate in the vicinity of these structures, which are well supplied with blood vessels The histologic picture is sometimes suggestive of both lymphocytic leukemia and lymphosarcoma and, occasionally, histologic differentiation is not possible Many contemporary investigators are of the opinion that lymphocytic leukemia and lymphosarcoma are the same disease, the only difference being that there is



Figure 116 Lesion of long duration, showing absence of glandular structures

metastasis to the blood stream in lymphocytic leukemia

The fundamental cells are mainly lymphocytes and, in chronic lymphocytic leukemia, they are of mature type The purity of the type of cell is highly important in the diagnosis of this disease The epidermis reacts not at all or only in a minor nonspecific and secondary manner

The significant features are present around the blood vessels and may extend to the deepest parts of the corium The densely packed lymphocytes are so numerous that extremely broad mantles are present around the blood vessels Although similar mantles may occur in many inflammatory dermatoses, edema is then also present and the epidermis is more or less acanthotic

There appears to be no histologic difference between the acute and chronic forms of leukemia in the hematopoietic tissue and no essential difference between leukemic and "aleukemic" leukemia In all cases of leukemia, whether chronic, acute, or "aleukemic," the essential findings are marked by proliferation of immature cells in either the bone marrow or

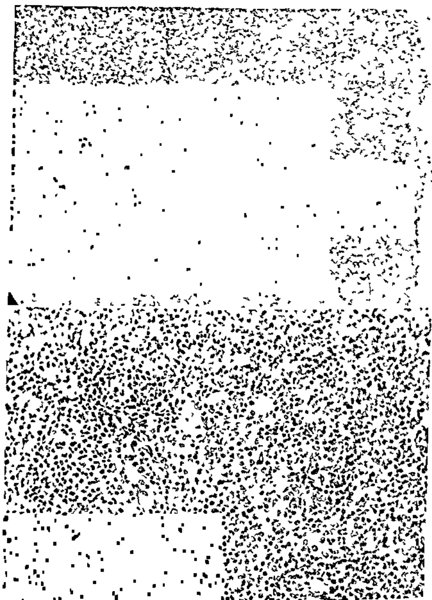


Figure 117 Lymph node composed almost entirely of lymphocytic cells (low power)

Figure 118 Lymph node composed almost entirely of lymphocytic cells (high power)



Figure 119 Mature lymphocytic cells

the lymphatic system and the formation of immature hemato poietic tissue in the liver and spleen Szilard (671) found that in "aleukemia" these immature cells were very fragile and

Figure 120 Absence of any reactive process in the epidermis

Figure 121 Lymphoblasts comprising the entire infiltrate

broke down as soon as they entered the peripheral circulation

A diagnosis of the type of leukemia present is dependent upon the recognition of the particular cell type present in fixed tissue sections in contrast to study of the blood smear Sometimes touch smears made by touching the specimen of tissue against a glass slide are of definite value particularly in cases of primary cutaneous leukemia when the peripheral blood changes are not yet demonstrable Although the infiltrate is composed almost entirely of lymphocytes lying in a very fine reticular connective tissue there are occasional large cells having nongranular basophilic cytoplasm and large round, lobulated oval or kidney shaped pale staining nuclei which occupy almost the entire cell (lymphoblasts) Plasmacytes are usually not present although one or two may occasionally be noted Occasionally mitoses of the lymphoblasts are found but mitotic figures involving the small lymphocytes are not present This is of interest in view of the extraordinary abundance of these cellular elements Pigment in the form of extracellular granules or clumps is found with in the tumor or on its borders

The blood and lymph spaces also show noteworthy changes On the borders of the nodes both the blood and lymph vessels show thickened walls and are markedly dilated The blood vessels are usually engorged with blood while the lymph vessels appear as large empty spaces Within the more central portions of the infiltrate there are many newly formed vessels which are either partially filled with a thrombus composed of small lymphocytes or contain numbers of red blood cells polymorphonuclears prolymphocytes and lymphocytes The walls of the arteries seldom show changes while the capillary and venous walls are densely infiltrated with lymphocytes and they may be entirely destroyed in some places The upper border of the infiltrate ends abruptly in an even line and it is separated from the epithelium by a narrow zone which has not been invaded by the tumor The connective tissue in this zone is practically normal but small amounts of polymorphonuclear infiltration and a few chromatophores

Figure 122 Engorgement of blood vessels with blood while the lymph vessels appear as large empty spaces (low power).

Figure 123 Engorgement of blood vessels with blood while the lymph vessels appear as large empty spaces (high power).



Figure 124 Many newly formed blood vessels

Figure 125 Diffuse type of leukemic infiltrate (Low power)



Figure 126 Diffuse type of leukemic infiltrate (High power)

are usually present around blood vessels which are moderately dilated There are more or less numerous mast cells present around the periphery



Figure 127 Absence of border zone between infiltrate and epidermis in leukemic exfoliative dermatitis (compare with Figure 107)

A diffuse type of infiltrate may be present in lymphocytic leukemia When this occurs, there is no tendency toward the formation of cutaneous nodules As this infiltrate progresses, strands of cells tend to push aside the connective tissue fibers

The correct diagnosis of leukemia cutis is dependent upon the presence of (1) an infiltration of lymphocytes which are mainly perivascular, (2) a deep infiltration, and (3) no inflammatory phenomena such as edema, leukocytic infiltration and acanthosis The monomorphous type of the infiltrating cells is striking and they are of great importance

Lymphocytic Leukemic Exfoliative Dermatitis. The entire epidermis is usually atrophic and covered by a somewhat thickened horny layer However in the early stages it may not be atrophic The border zone of normal connective tissue between the infiltrate and the epidermis is not present In the papillary and subpapillary layers of the cutis there is either a diffuse infiltrate, sharply limited on its lower border, or a nodular infiltrate arranged around the blood vessels and the

Figure 128 Infiltrate composed of lymphocytes and fibroblasts

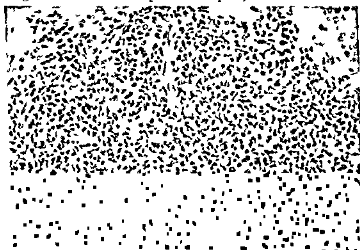


Figure 129 Infiltrate showing many neutrophilic and eosinophilic granulocytes

sweat glands The infiltrate for the most part, is made up of lymphocytes and a few fibroblasts The lymphocytes have a definite perivascular arrangement, while the fibroblasts are

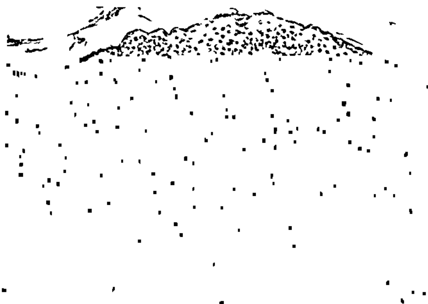
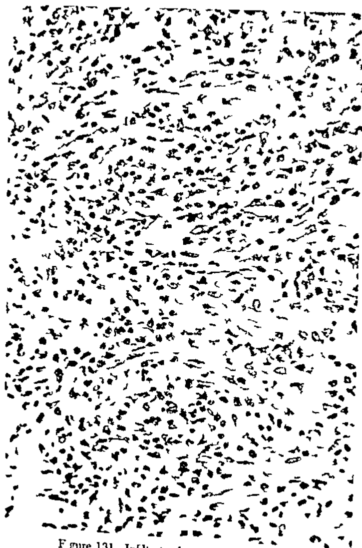


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F gure 131 Infiltrate showing m totic figures

distributed in a more diffuse manner throughout the entire area In many cases there may be a considerable number of mast and pigment cells present The latter are often arranged in an encircling band on the borders of the nodes of infiltration

Granulocytic Leukemia The infiltration is composed of neutrophilic and eosinophilic granulocytes rubriblasts rubricytes giant cells mast cells and lymphocytes There is a tendency toward immaturity of the cells and often an increase in eosinophils so that some investigators refer to an "eosinophilic lymphoblastoma Mitoses are rather frequent more so than in lymphocytic leukemia The cells are usually large relatively pale staining monocytic cells which contain many granules They comprise the granulocytic series of cells in varying degrees of immaturity from the myeloblast through the three stages or ages of myelocytes all immature polymorphonuclears The giant cells which may be atypical fibroblasts are phagocytic in nature as they often contain nuclear remnants Megakaryocytes have been observed in the cutane-



Figure 130 Infiltrate showing many neutrophilic and eosinophilic granulocytes



Figure 134 Location and distribution of infiltrate in granulocytic leukemia showing a similar distribution to that in lymphocytic leukemia

Figure 135 Location and distribution of infiltrate in granulocytic leukemia showing a similar distribution to that in lymphocytic leukemia

Figure 132 Large pale staining monocytic cells

Figure 133 Location and distribution of infiltrate in granulocytic leukemia showing a similar distribution to that in lymphocytic leukemia

are particularly liable to involvement

Cutaneous infiltration by monocytes, together with hemorrhage, has been described *many times* These findings were reported in detail by L A Mitchell (456), Osgood (496a), Klumpp and Evans (345), Schilling (605a), Sydenstricker and Phinizy (669) and Whitby and Christie (725b) Hemorrhage, ulceration, and conspicuous lack of granulocytes in lesions of the mucous membranes, were described by Bingel (47), Hittmair (288), Orr (495), Schilling (605b) and Wyschegorodzewa (746) As in acute forms of the disease, most of the internal organs become infiltrated by monocytes and involvement of the spleen, liver and lymph nodes often occurs Among patients who survived for 30 weeks or more, cutaneous hemorrhage was noted by Bohne and Huismans (60), Dubinskaja and Bakaltschuk (154), Foot and Olcott (191), Forkner (192a), Giffin and Watkins (224), Klumpp and Evans (345), Komiya and Hayashi (350), L A Mitchell (456), Orr (495), Osgood (496a), Roversi and Salaris (585), Swirtschewskaja (667), Sydenstricker and Phinizy (669), Whitby and Christie (725b), and others. Ulceration of the skin and mucous membranes has also been noted by many investigators, among them Dorn and Wiseman (149), Dubinskaja and Bakaltschuk (154), Farley (179), Foot and Olcott (191), Forkner (192a), Klumpp and Evans (345), Komiya and Hayashi (350), L A Mitchell (456), Orr (495) Osgood (496a), Powell (537), Roversi and Salaris (585), Swirtschewskaja (667), Sydenstricker and Phinizy (669) and Whitby and Christie (725b)

Herbut and Miller (277) found that the monocytic cells which occurred within vessels were more uniform than those in the infiltrating tissues These cells, one and one-half to three times the diameter of erythrocytes, were round or oval in shape and their borders were usually distinct and sharp, but occasionally they were "ill defined and fuzzy." The cytoplasm, which occupied one eighth to three fourths of the cell volume, stained deep pink with hematoxylin and eosin but light blue with Giemsa stain The cytoplasm was pro

ous tumors Ketron and Gay (338b) noted a peculiar nuclear degeneration of the eosinophils Clear cut oxydase reactions are seldom obtained in cutaneous sections, and in many cases the reaction has been reported to be negative The location and distribution of the infiltrates are about the same as in lymphocytic leukemia

Monocytic Leukemia. In the Schilling type of monocytic leukemia the monocytes develop directly from the endothelial cell, whereas in the Naegeli type they develop from the myeloblast or stem cell In the Schilling type chromatin strands become thick and produce what appears to be a grooving of the nucleus This grooving persists to the stage of complete maturity of the monocyte and sometimes permits histologic distinction from the Naegeli type in which the monocytes show indentation and do not have the prominent grooving Hemocytologic studies are usually necessary for differentiation In all types of 'lymphoblastoma,' except lymphocytic leukemia, there is an increase in reticular fibers, and in all forms of 'lymphoblastoma' there is destruction of the elastic tissue in areas of infiltration

The infiltrate is loosely arranged, except around the blood vessels and sweat glands, and is made up of atypical spherical monocytic cells There is a definite tendency for linear arrangement of the cells

The outstanding pathologic processes observed at autopsy are hemorrhage, ulceration and hyperplasia of the reticulo endothelial system, according to Evans (172i) Hemorrhage was present in nearly all cases and cutaneous hemorrhages have been described by numerous observers There are also many reports of purpura and petechiae Schultz and Kruger (612) believed the hemorrhagic diathesis to be very evident Hemorrhage from some area of the oral cavity occurs fre quently and the gums appear to be the area most frequently involved Bleeding from the stomach is not infrequent The pleura, pericardium, peritoneum meninges and kidneys have also been found to be hemorrhagic, according to Lawrence *et al* (373d), who stated that the gums and buccal mucosa

in some of the more immature cells but they could not be definitely identified with hematoxylin and eosin stain There were numerous mitotic figures among the immature cells but they were less frequent or absent among the more mature monocytes

Several investigators have noted a striking histologic similarity between subacute and chronic monocytic leukemia and Hodgkin s disease They have cited the cases described by Doan and Wiseman (149) Evans (172a) Dameshek (139b) T B Mallory (423) and Herbut and Miller (277) as examples of this similarity

Loveman (398) pointed out that the infiltrate extends between the strands of connective tissue but does not destroy them as in other types of leukemia The cytoplasm of the invading cells is usually slightly basophilic and vacuolated and shows considerable variation in amount and density The nuclei are large often idented or kidney shaped and have well defined strongly basophilic nuclear membranes and clear basophilic or neutrophilic pale-staining nucleoplasms There were one or two large basophilic nucleoli in the nucleus He also mentioned that there was a lack of practical value in the application of the oxydase reaction to tissue removed from patients with monocytic leukemia

F W Lynch (409i) believed the pathologic changes observed in specific cutaneous lesions of monocytic leukemia to be rather characteristic The epidermis is normal or nearly normal while in the earlier lesions cellular infiltration is present mainly in the perivascular areas and surrounding the appendages The diagnostic feature he believed was in the character of the infiltration the reaction consisting primarily of mature and immature monocytes There are large cells which have an abundant cytoplasm The immature forms have a dark reniform or bilobed nuclei while the more ma

[illegible]

[illegible] observer could recognize that the polymor

portionately more abundant and contained phagocytosed nu clear material brown pigment and erythrocytes The round oval and irregular nuclei were usually rather large The ir regularly shaped nuclei often had a single indentation re sulting in a typical horse shoe shape but they frequently con tained two or more deep indentations giving the appearance of definite lobulations The nuclear material was occasionally found to be twisted upon itself making it difficult to dis tinguish the convolutions Although the nuclear margins were always found to be distinct the nucleoplasm usually stained very lightly and contained small irregular aggregations of *chromatin which were sometimes connected by fine almost* imperceptible threads Nucleoli were not found in any of the intravascular monocytic cells In tissues the cells showed con siderably more pleomorphism Those which were more ma ture and less tightly packed closely resembled those in the pulmonary alveolar exudate and peripheral blood but those which were less crowded and less mature showed all grada tions from large spindle shaped polyhedral or irregular forms which are readily indistinguishable from ordinary reticulum cells Frequently there were long thin fibrillary processes which projected from the angles of the more irregular cells which were directly continuous with the supporting reticulum At other times the sinus endothelial cells particularly those of the bone marrow were swollen and showed various degrees of intravascular and extravascular detachment causing the cytoplasm to be completely separated All the cells had sim ilar staining qualities although they varied in size and con figuration *while in the reticular cells more immature spindle* and irregular monocytic cells they were considerably larger *than in the round and circulating monocytes* They were fre quently of irregular shape and assumed triangular and rec tangular configurations There were few twists and inden tations and they were rarely of horseshoe shape Occasion ally one or two separate nuclei appeared to be piled up in a single cell to produce cells which closely resembled Stern berg Reed cells Giemsa staining revealed one or two nucleoli

Large, round, oval or polygonal monocytes some having long processes which extended into the reticular network, were noted between the fibrils There was a large, round or oval shaped nucleus and the cytoplasm and nuclear structure stained lightly These cells appeared to be closely related to the reticular framework There were also round cells which had a dark staining small, eccentric nucleus, and many large clear cells having a moderately dense, reniform or bilobed nucleus and which resembled intermediate forms in the monocytic series Herbut and Miller stated that stains for elastin are of little value in the study of these diseases since they indicate only the absence of elastin fibers in the infiltrated and granulomatous areas and degeneration of these fibers in the corium at the border of the pathologic process The large giant cells which are observed in some cases of reticuloendo thel[illegible] do not appear to be of an [illegible]

In one of Herbut and Miller's (277 case 1) patients, histologic examination of the gums revealed the mucosa to be intact and normal except for some vacuolization of the prickle cell layer The immediate subjacent submucosa was edematous but contained only a few empty capillaries and was sparsely infiltrated with round or oval monocytes However, in the deeper tissues the densely packed monocytes obliterated all normal structures except for a few strands of striated muscle In these areas the monocytic cells were polygonal and quite irregular Only a few widely separated and insignificant foci of extravasated erythrocytes were present throughout these sections

phous cellular infiltrate is different from that of other pathologic processes Monocytic leukemia can be differentiated from lymphocytic leukemia by the large size of the cells and the notching of the nuclei Differentiation from Hodgkins disease can be made by the absence of Sternberg Reed cells and eosinophils

A series of 50 cases of acute monocytic leukemia (Schilling) were reviewed by Hubler and Netherton (298) They noted *that the epidermis was not usually involved unless ulceration* occurred A narrow band of corium which separated the epidermis from the tumor tissue was sometimes present and an increase of reticulum was observed The cellular infiltrate was invasive consisting of large nodules composed of closely packed cells and it frequently occurred around a dermal appendage or blood vessel

The reticular proliferation and intermediate cell forms observed in the skin of patients with monocytic leukemia and reticuloendotheliosis may be regarded as further support for the view that the specific cutaneous lesions of leukemia develop *in situ* and are not the result of metastases or infiltration from the blood stream according to Herbut and Miller (277) There appears to be fairly general agreement concerning the pathology of the cutaneous lesions occurring in reticuloendotheliosis The changes in the epidermis are secondary to disturbed nutrition Reticular proliferation of the cutis and infiltration of monocytes are pathologic changes also *found throughout the reticuloendothelial system in these* diseases Among the cases reported by Herbut and Miller the early cutaneous changes appeared around the vessels and cutaneous appendages and consisted of infiltration with small lymphocytes and polymorphonuclears The observations were not specific at this stage of the disease but later the involvement became most marked in the lower portion of the cutis and extended into the subcutaneous tissue The fibrillary structure was replaced by a reticular network which resembled embryonic mesenchymal tissue and the supportive tissues no longer resembled collagenous connective tissue

some cases which have certain morphologic lesions These cases are, therefore, true "ids" (1) Prurigo like papules, (2) vesicobullous lesions, (3) purpura, and (4) erythematomacular lesions

Prurigo-Like Papules. Parounagian (504) reported a 52 year old woman who had intensely pruritic cutaneous lesions consisting of multiform papules, vesicles and urticaria which primarily involved the extremities She presented the typical clinical picture of dermatitis herpetiformis Histologic examination of the skin revealed a "leukemic process" according to Highman (281a) The hemogram disclosed lymphocytic leukemia A 63 year old man, reported by Opfer (491), had chronic "aleukemic" myelosis which simulated Duhring's disease He had splenomegaly, but the peripheral blood count was "relatively normal" There were multiple pigmented cutaneous nodules which simulated those of Duhring's disease Histologic examination of the lesions revealed chronic "aleukemic" myelosis with polymorphonuclears, eosinophils and cells which resembled myelocytes and myeloblasts The oxydase reaction was strongly positive The herpetic and urticarial zones around the cutaneous lesions were believed to result from "toxic by products" from the leukemic area

Vesicobullous Lesions A 68 year old man who had lymphocytic leukemia associated with bullous cutaneous lesions was presented by MacKee (416) Bullae first appeared on both feet, then on the arms, and finally on the head The bullae were present for about one month before "drying up" Histologic examination of a bulla was reported to show lymphocytic leukemia M Wolf and Gounelle (742) reported a 65 year old man who presented cutaneous leukemids during the course of lymphocytic leukemia The lesions were deep infiltrations with a vesicle containing clear fluid, involving the arms forearms and hands The hemogram revealed 40 000 white blood cells per cu mm, with 95 per cent lymphocytes Histologic examination of a cutaneous lesion disclosed lymphocytic leukemia

Purpura A 62 year old man, reported by Almkvist and

IX

LEUKEMIDS

Leukemids ("Ids"). In leukemia, there appears to be no definite distinction between the toxic or nonspecific cutaneous lesions and true tumors, or specific cutaneous lesions The unity of these two conditions, which frequently cannot be separated clinically or pathologically, was often apparent in the reported cases The two conditions may merge impercep tibly The connecting link between these two disease groups are the "ids" (leukemids, when associated with leukemia) Clinically, they resemble nonspecific or toxic cutaneous le sions, but histologically they resemble specific or true cutane ous infiltration by leukemic cells

All toxic cutaneous eruptions were designated as "ids" by Audry (18) but, in my opinion, this grouping is incorrect This fact was well illustrated by Highman (281b) who point- ed out that "syphilid' is used to designate a lesion due to the treponema pallidum and has the histologic structure of the syphilitic infiltration When the term "lepride" is used, the same significance is attached to the lesion so designated, but with reference to Hansen's bacillus True leukemia of the lymph nodes has a distinct histologic structure and a 'leu kemid" should show the histologic picture typical of the dis ease It seems incorrect to group all toxic or nonspecific cu taneous lesions associated with leukemia as "ids" However if a toxic eruption also has the specific histologic picture of leukemia, it should be called "leukemid' and not a "toxic eruption"

A specific histologic picture of leukemia may be present in

dyspnea Purpuric "spots" then appeared on the left ear, left hand thumb and ring finger, and on both lower extremities Histologic examination of a purpuric lesion showed leukemic infiltration of the skin



Figure 138 Purpura Histologic examination revealed the specific picture of granulocytic leukemia

Erythematomacular Lesions The patient presented by Bouchut *et al* (68b) had a disseminated eczematoid dermatitis with small papillary tumors which resembled a "vegetating" type of dermatitis involving the arms and lips Histologic examination disclosed lymphocytic leukemic infiltration of the skin

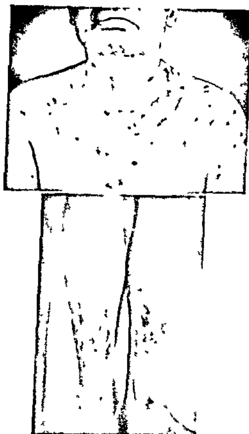


Figure 136 Purpura Histologic examination revealed the specific picture of granulocytic leukemia (*A M A Arch Dermat*, 73 189, 1956)

Figure 137 Purpura Histologic examination revealed the specific picture of granulocytic leukemia (*A M A Arch Dermat*, 73 189, 1956)

Arzt (5), first had lymphadenopathy in the left supraclavicular region and a diagnosis of lymphocytic leukemia was established Isolated, "dot shaped" cutaneous hemorrhages, most marked on the extremities, then appeared At autopsy, there was leukemic infiltration of the lymph nodes, spleen and liver Histologic examination of the skin revealed lymphocytic leukemia D Angelo and Cicala (141) reported a 43 year old man who first had pain in the chest, cough and

be cleansed out after meals by use of dilute hydrogen peroxide (1 1/2 per cent) mouth wash which will help to remove mechanically debris from sulci and between teeth The gingiva may be cleansed by swabbing with cotton swabs moistened with hydrogen peroxide (2 3 per cent) or sodium bicarbon ate solution Calculus and faulty restorations should be care fully eliminated with trauma kept at a minimum These pro cedures may occupy a week or two After each visit at which calculus or other irritants are removed the gingiva should be treated by application of a broad spectrum antibiotic solution or if the consulting physician prefers by systemic adminis tration of such antibiotics Under such therapy a severe in flamed mouth of a leukemic patient may be returned to nearly normal conditions If the patient is seen before oral lesions develop the mouth should be meticulously freed of irritants and thorough oral hygiene instituted"

In chronic leukemias Robinson (568) found the symptoms to be less striking An unexplained lymphadenopathy may be the first symptom followed by gradual weakness anemia and dyspnea Intraoral lesions of hemorrhage either petechiae or ecchymoses may occur and the resistance of the peridontal tissues may be lowered and lead to gingivitis or periodontitis "As in the acute leukemias the differentiation of types is not based on the oral appearances which are only the results of cellular infiltration and lowered resistance to infection"

Monocytic Leukemia There appears to be a markedly high er incidence of mucocutaneous involvement in monocytic leu kemia than in either lymphocytic or granulocytic leukemia According to the reported incidence mucocutaneous lesions occur in about 50 per cent of the cases of monocytic leukemia These lesions may be specific nonspecific or both types may occur simultaneously However they are not considered to be pathognomonic of the disease The gums may become hyper trophic with necrosis and ulceration of the oral mucosa and hemorrhages of the membranes may occur

Among 152 patients having various types of leukemia Love (397) found 82 patients had oral lesions The most frequent

X

ORAL LESIONS

THE EARLY oral symptoms of leukemia vary, according to Thoma and Robinson (680b), and have been described differently by investigators who have observed different groups of patients (Armbrecht and Apple (13), T J Cook (120), Thoma (680a) and Wentz (721)) In reviewing stomatitis occurring with blood dyscrasias, Robinson (568) found that the most prominent features were usually enlargement of the gingiva and large areas of ulceration extending from the gingiva onto the palatal, buccal or labial regions, or into the floor of the mouth The marked gingivitis may be of diagnostic aid in the early stages of the severe underlying disease Spontaneous bleeding and hemorrhage were present in about one third of the patients with acute leukemia studied by Wentz (721) Pallor of the noninflamed regions of the oral mucosa may also occur There are reports of changes in the pulp of noncarious teeth of leukemic patients which accounts for the severe toothache these patients sometimes experience (Burket 86)

The enlargement of the gingiva is due to engorgement of leukemic cells in the gingiva and to edema which accompanies the blocking of blood vessels and the inflammation, according to Robinson (568) "The gingival tissues become inflamed and necrotic because of the reduced cellular (leukocytic, lymphocytic, monocytic) defense against irritations from calculus, faulty dental restorations and the ever present oral microorganisms For this reason removal of all irritants is of primary importance If gingivitis exists, the mouth should

casionally was not associated with infection He found that a great many patients consulted a dentist for tooth extraction before seeking medical care It was his opinion that because of the high incidence of gingival swelling in monocytic leukemia this disease should always be considered when this symptom is present Forkner (192a) considered this diffuse marked swelling of the mucous membranes particularly the gingivae with ulceration and necrosis to be characteristic of monocytic leukemia However Court and Edward (128) found that severe oral involvement was not a characteristic feature of monocytic leukemia occurring in children, but it was merely a suggestive symptom They noted that oral lesions occurred in 52 per cent of all cases of monocytic leukemia and in 20 per cent of the children with monocytic leukemia These lesions consisted of soreness bleeding of the gingivae and swelling and necrosis of the mucous membrane which may extend to involve the tonsil or soft palate Although these lesions may cause some of the striking symptoms which occur in adults such as necrosis resulting in diffuse cellulitis they found that only the milder forms occur in children It was a prominent feature in only two cases Although this involvement was the presenting symptom in a patient described by Ernandez (169 case 1) the other reported cases showed only simple bleeding and superficial ulceration a terminal feature in many cases Jaffe (314b) stressed that the tonsils are particularly likely to be the site of origin of tumor like infiltrations in the subleukemic type of leukemia

Netherton and Curtis (473b) described a 19 year old woman who first had diarrhea and painful hypertrophy of the gums Several months later a large ulcer which had a necrotic center appeared on the left margin of the hard palate Many of the teeth were barely visible due to the marked hypertrophy and swelling of the gums Another patient who had oral lesions associated with monocytic leukemia was also reported by Curtis (136)

In a review of this subject Evans (172a) found that the greater majority of cases reported mentioned the occurrence



Figure 139 Hemorrhagic lesions of the gums associated with acute monocytic leukemia

Figure 140 Hemorrhagic lesions of the tongue associated with acute monocytic leukemia

symptoms were bleeding gums and swelling, ulceration and necrosis of the gingivae Osgood (496a) found swelling of the gums to be one of the most constant features of the disease, occurring in 80 per cent of 88 cases These symptoms were more marked and constant in monocytic than in the acute forms of other types of leukemia The swelling was frequently associated with gangrenous stomatitis, similar to the type which occurs in agranulocytosis, although this swelling sometimes preceded the development of infection and oc-

mucocutaneous junction on the right side of the mouth Another patient, a 60 year year old woman, presented marked pallor and cyanosis and numerous purpuric and petechial spots over the entire cutaneous surface Numerous petechial hemorrhages into the skin and mucous membranes were noted at autopsy

Among 14 cases of monocytic leukemia, Mann (424) found that stomatitis was the initial symptom in 60 per cent of the cases and some degree of stomatitis ultimately occurred in 80 per cent of the cases He described a 57 year old man who had sore throat and malaise for five weeks He had a small necrotic ulcer around the root of the last upper molar tooth on the right side and the tooth was extracted However, three days later he had gangrene of the right side of the palate which extended to the anterior pillar of the tonsil He became emaciated and incoherent There were nine or 10 dull red raised cutaneous nodules, about 2 5 cms in size, involving the arms, neck and chin There were one or two [illegible] The hemogram [illegible] red blood cells [illegible] r cu mm, with 69 to 81 per cent monocytes and a "few blood platelets" The patient died five days after extraction of the tooth and autopsy revealed numerous plaque-shaped leukemic deposits, some 4 cms thick, present in the skin A foul gangrenous stomatitis extended to the epiglottis, the spleen was enlarged and the bone marrow was found to be filled with monocytes, on histologic examination

McCarthy and Karcher (411b) found oral lesions to be a frequent, early symptom in leukemia, particularly in the acute form of the disease Monocytic leukemia represents five per cent of all leukemic cases, they stated, and in this type an extremely high incidence of gingival and other oral changes occur in patients who are edentulous They found that gingival hyperplasia with edema, necrosis and a tendency to bleed from the gums, occur either spontaneously or from slight trauma However, gingival hyperplasia may occur in

of ulceration and bleeding of the gums This was very often the presenting symptom and the dentist was first consulted for extraction of teeth but the frequency of intractable bleeding led to consultation with an internist He found that throat lesions were not as common as those of the gums although ulceration and angina have frequently been described Among eight cases of monocytic leukemia reported by Klumpp and Evans (345) the symptoms first appeared following dental extraction in five and following severe trauma in two cases Their patients ranged from 12 to 74 years of age the latter they believed to be the oldest patient to be reported Another of these patients was a Negro whom they believed to be the second Negro patient on record the other having been described by Levine (385) They concluded that oral lesions occur frequently in acute leukemia usually early in the course of the disease One of their patients a 65 year old Negro had numerous isolated purpuric areas on the skin and hemorrhagic spots on the mucous membranes of the mouth and tonsils The gums were edematous and bled easily while the enlarged tonsils were of a peculiar grey color with small patches of greenish grey exudate Another patient a 23 year old woman had isolated purpuric spots and areas of ecchymoses scattered over the cutaneous surface and a mottled brown discoloration of the neck and abdomen which they stated may have resulted from arsenotherapy Dry crusted ulcerations were present at the angles of the mouth and the oral mucous membranes were edematous The tonsils which were swollen and edematous had the appearance that is occasionally seen preceding ulceration They described a 56 year old man who had spontaneous suppurating ulcers on the lateral aspect of the right thigh and ankle These lesions healed promptly but a similar persistent ulcer had occurred following trauma three weeks previously Two weeks later he was injured and pain weakness and fever developed He presented a few purpuric spots diffused over the cutaneous surface and a suppurating ulcer over the left external malleolus A 5 cm ulcer having a dry brownish crust involved the

plastic gum tissue formed and the teeth tended to migrate and assume "fantastic proportions" indicating destruction of the alveolar lamina dura Histologic study of the interdental papillae showed the outer labial stratified epithelial surface to be thinned especially in the prickle cell layer The underlying tunica propria was considerably edematous and showed increased vascularity There was a wide zone of edematous fibroblastic connective tissue which was moderately infiltrated with monocytes (50 per cent of the cells) lymphoid type cells and polymorphonuclears The deeper layers were less edematous more pronounced and there were numerous foci of hemorrhage Rich bacterial flora and Vincent s organisms were demonstrated in this area At autopsy, the skin and sclerae were moderately icteric and there were purpuric and petechial hemorrhages involving the forearm and face particularly the alae nasi as well as hepatosplenomegaly

According to Forkner (192a) acute swelling of the gingivae with a tendency for the teeth to become submerged in the gums occurs in the great majority of cases However infiltrated lesions of the gums are not always pathognomonic of acute monocytic leukemia

Hall (253) described a 63 year old woman who first had a nontender swelling on the right side of the tongue accompanied by scattered aphthous ulcers The swelling on the tongue gradually enlarged and a small ulceration developed near the center followed by similar swelling and ulceration of the left tonsil One month later small red cutaneous macules appeared on the outer aspect of the lower left leg and [illegible]

[illegible] tumor involving the right anterior one third of the tongue which bulged at the sides and top surface The left tonsil appeared to have involvement similar to that of the tongue and there was a small discrete lymph node palpable just below the angle of the left mandible There were aph

diseases other than monocytic leukemia and, therefore, drug reactions (including that from Dilantin®), Vincent's angina, aplastic anemia, agranulocytosis and infectious mononucleosis, as well as pregnancy, must be considered in the differential diagnosis They found one of the major sources of pain and discomfort associated with monocytic leukemia to be due to the necrotic, ulcerative lesions which involve the gingivae and buccal mucosa In their opinion, all cases of gingival hyperplasia *with bleeding and a tendency to necrosis, with* secondary Vincent's infection, should have hematologic examinations to rule out serious blood dyscrasias They described a 27 year old woman who had progressive involvement of the oral mucous membranes during the entire course of the disease The hyperplastic gum tissue increased in size along the labial and lingual surfaces of the alveolus The entire arch became broad and consisted of swollen, edematous, necrotic, vascular gingival tissue which gradually obscured the teeth Three or four weeks later a secondary growth of hyperplastic tissue developed at the base, which followed the same pattern as that in the outer layer, and increased to the width of the alveolus until the palatal vault was nearly eliminated The floor of the mouth was partially filled with vascular, necrotic gingival tissue which caused the tongue to be raised and the mouth could not be closed The mouth was extremely dry, partly from evaporation, and new superficial necrotic lesions, with secondary gangrenous changes, developed on the mucosa of the lateral margins of the tongue and buccal mucosa of the cheeks These lesions were covered by a pale yellow *pseudomembrane which left a raw, bleeding surface* when removed An ulcerated lesion was present on the right lateral palatal region near the first molar tooth and another on the left side of the soft palate extended to the anterior pillar of the fauces A fairly generalized petechial purpuric, macular eruption appeared on the buccal mucosa and similar hemorrhagic cutaneous lesions on the face four days before death, while inspissated *blood, mucus, detritus and exudate formed* a "hard shell" on the dorsum of the tongue Secondary hyper-

which were predominantly immature monocytes The diagnoses were (1) acute monocytic leukemia (2) leukemia cutis, (3) secondary anemia, and (4) ulcerative leukemic stomatitis He died a few days later Aseltine believed that patients having blood dyscrasias have decreased or little resistance against infection following tooth extraction and local necrosis results Because the leukocytes are immature and unable to combat infective organisms, surgical intervention is definitely contraindicated

The patient described by Boyd Cooper (71) had ulcerative stomatitis associated with subacute monocytic leukemia We have observed a 72 year old man who first presented a 3 cm nodule on the palate which became ulcerated within two to three weeks time A detailed report of this case appears under Specific Lesions (Chapter V)

The frequent occurrence of tumefaction of the gums and ulcerative lesions of the mouth in monocytic leukemia was stressed by A C P Campbell *et al* (94), Dameshek (139a, b) L. A Mitchell (456), and others Patients having these oral lesions have also been described by Farrar and Cameron (180), Foord *et al* (190), and F W Lynch (409a case 6) However, Jaffe (314f) and Wintrobe (737a) shared the opinion of Watkins and Hall (710b) that these changes *in the* gums are not characteristic, or exclusively representative of monocytic leukemia

A child who had painful hemorrhagic gingivitis associated with other symptoms of acute leukemia was described by Fiorentini (185) Histologic examination of the gums disclosed leukemic infiltration, particularly in the perivascular region Forkner (192b) believed this case to be one of acute monocytic leukemia

Among six patients with acute monocytic leukemia reported by Forkner (192a), all presented swelling of the gingivae, with subsequent ulceration and necrosis, as the first symptom of leukemia All of these patients first consulted a dentist before seeking medical advice Forkner believed that, contrary to the statements made in textbooks and other medical pub-

thous ulcers scattered over the buccal lining Watkins and Hall (710b) did not believe the changes in the gums to be characteristic or exclusively representative of monocytic leukemia In their series, however, three of nine cases of acute and two of 14 chronic cases of the Naegeli type had involvement of the gums, while none of the six Schilling type cases had this involvement

Among nine cases of monocytic leukemia, Moloney (458) found the initial symptoms in seven cases to be bleeding gums, "trench mouth," or pain of the jaw He believed that palliative treatment and avoidance of injudicious oral surgery would make the patient much more comfortable

Among the patients described by Herbut and Miller (277), one (case 1) had marked hypertrophy of the gingivae, which completely covered the lateral surfaces of the teeth in some areas The mucosa was covered with coagulated blood and the underlying pinkish-grey tissue was moderately firm There were numerous petechiae in the mucous membranes of the upper lip and left cheek Another patient (case 5) presented necrotic, nonhemorrhagic areas scattered throughout the mouth, most marked over the gums Two other patients (cases 2 and 4) showed bright red, recently coagulated blood on the mucous membranes of the mouth particularly on the gingivae Superficial erosion of the tip of the tongue occurred in one patient (case 3) There was a large ulcer, with a floor containing soft necrotic tissue and a reddish base, involving the inner portion of the left cheek and adjacent gums

A 66 year old man described by Aseltine (17), had a "sore mouth" and Vincent s infection for eight weeks There were several markedly tender, large ulcers involving the gingival tissues and mucobuccal fold which had an irregular periphery and marginal inflammation There was submaxillary, cervical and bilateral inguinal lymphadenopathy and hepatosplenomegaly Painless, elevated, indurated areas, surrounded by hemorrhages, involved the trunk and extended down the legs The hemogram revealed 51 per cent hemoglobin, 2,100,000 red blood cells and 102,000 white blood cells per cu mm

which were predominantly immature monocytes The diagnoses were (1) acute monocytic leukemia, (2) leukemia cutis, (3) secondary anemia, and (4) ulcerative leukemic stomatitis He died a few days later Aseltine believed that patients having blood dyscrasias have decreased or little resistance against infection following tooth extraction and local necrosis results Because the leukocytes are immature and unable to combat infective organisms, surgical intervention is definitely contraindicated

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of [illegible]
to [illegible] advice Forkner believed that, contrary to the statements made in *textbooks* and other medical pub-

lications on acute leukemia, the mouth lesions present in acute monocytic leukemia are usually different from those which occur in other types of acute leukemia In acute monocytic leukemia, diffuse swelling of the gingivae with a tendency for the teeth to become submerged in the gums occurs in the great majority of cases Associated with this, there is what appears to be a diffuse cellulitis which causes pain, and signs of acute inflammation extending into the deeper layers of the tissues of the face In one of Forkner's cases, histologic study of the involved gingivae showed diffuse infiltration with leukemic cells The mouth lesions which occur in acute lymphocytic and acute granulocytic leukemia, however, do not usually exhibit these characteristics Bleeding from the gums is frequent in all types of acute leukemia Ulceration, resulting from trauma, hemorrhage and secondary infection often with Vincent's organisms, may also occur in any type of leukemia However, the characteristic signs and symptoms in the mouth usually distinguish acute monocytic leukemia from the other forms of acute leukemia according to Forkner

Lymphocytic Leukemia. The intraoral lesions of chronic lymphocytic leukemia are classified as (1) hemorrhagic manifestations, (2) inflammatory ulcerative necrotic lesions, and (3) infiltrative or tumor like lesions, according to Bluefarb and Rodin (56h)

Hemorrhagic Lesions The most frequent oral lesions are bleeding of the gums at the gingival margins The gums may be pale and of normal contour, in some cases, but others show hypertrophy and edema and simulate the gum lesions in scurvy or acute stomatitis The interdental tissues are entirely destroyed and the clinical picture sometimes resembles typical Vincent's infection according to Love (397) Warren (708) found Vincent's infection to be present in about 50 per cent of the cases This finding is probably not of etiologic importance, since prolonged bleeding from the gums, rather than their appearance, is a more important symptom The bleeding is characteristic since it appears to originate in apparently intact mucous membranes Frequently

uncontrol
eth Rarely
there may be bleeding ... of petechial hemorrhages superficial ecchymoses and deep hemorrhages The petechiae vary in size and usually involve the hard and soft palates or the buccal mucosa while the hemorrhagic lesions usually occur with thrombocytopenia

Ulcerative Necrotic Lesions Gangrenous stomatitis and large sloughing lesions may occur during the course of chronic leukemia The cutaneous ulceration usually follows the infiltrative stage of the mucous membranes particularly in monocytic leukemia Necrosis may occur on the buccal surfaces of the cheeks the labial surfaces of the lips the gums the hard or soft palate or on two or more of these areas although there appears to be no specific area of predilection Necrosis of the gum tissue usually begins around the posterior molars according to Love (397) probably because the gum cuffs are thicker and more extensive over these areas and from a mechanical standpoint are able to harbor more bacteria Necrosis of the gums does not necessarily indicate an acute phase of leukemia because this finding may be present in typical chronic leukemia without acute manifestations

Ulceration of the mucous membranes occurs frequently in chronic lymphocytic leukemia particularly in the terminal stages of the disease This ulceration may result from underlying leukemic infiltration of the tissues in some cases but in others may be due primarily to invasion of the mucous membranes by spirochetes and other pathogenic organisms in persons having a lowered resistance to infection

Infiltration Hyperplasia of the lymphoid tissue of the tongue pharynx and tonsils may occur in chronic lymphocytic leukemia Hypertrophy with irregularly raised nodular surfaces and nodular swellings may involve the gums The infiltrative lesions result from deposition or proliferation of abnormal cells The cell which characterizes the type of leukemia present may infiltrate the mucous membranes either locally or diffusely Leukemic lesions occur less frequently in

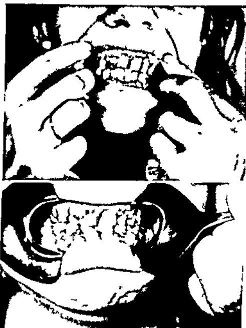


Figure 141 Infiltrations of the gum associated with chronic lymphocytic leukemia (*Eye Ear Nose & Throat Month*, *31* 309, 1952)

Figure 142 Infiltrations of the gum associated with chronic lymphocytic leukemia

the throat and are not as varied as those in the oral cavity When they do occur, there are usually painful, enlarged tonsils, where tumor like infiltrations of leukemic cells usually originate Tumor-like infiltrations of the upper respiratory tract, originating in the tonsils, in cases of "aleukemic" lymphocytic leukemia, were stressed by Jaffe (314b) He stated that unexplained tonsillar enlargement in elderly persons should always suggest the possibility of leukemia

A 67 year old man who had an ulcerative process in both tonsillar regions was described by Keim (333c) There was a distinct "mass," particularly on the right side, which caused bulging in the region of the anterior pillar The lesion was firm and painless and the mucous surface was ulcerated and bled freely on palpation



Figure 143 Infiltrations of the gum associated with chronic lymphocytic leukemia (*Eye Ear Nose & Throat Month* 31 309 1952)

The mucous membrane infiltration may extend to the pharynx and epiglottis This involvement is more frequent in chronic lymphocytic leukemia, particularly in the "aleukemic" form

Granulocytic Leukemia. Localization occurs much less frequently in the mucous membranes of the mouth in acute granulocytic leukemia than in the other acute leukemias Tumor formation, identical with the cutaneous involvement, has been described by Almkvist and Arzt (5), Arzt (16c), Barney (28b), Hartmann (261), Ketron and Gay (338b) and Tennenbaum (677) More frequent mucous membrane ulceration, in contradistinction to those on the skin, were described by Almkvist and Arzt (5), Tennenbaum (677) and Shigeruanan (631) The patient reported by Hartmann (261) had 2 to 3 mm swellings of the gums which reached the masticating surfaces of the teeth Confluent nodules in the buccal mucosa were described by Almkvist and Arzt (5), while Levin's (384a) patient had a labial herpes simplex

Isch Wall (309) reported a 54 year old man who had epistaxis and gingival hemorrhages The woman reported by Small and Schmidt (637) had soreness of the mouth as the initial symptom of leukemia A severe gingivitis and numerous white, raised, circumscribed necrotic lesions then appeared on the oral mucous membranes Cumming (133) reported a woman who first presented a completely denuded, painful tongue and numerous hyperkeratotic plaque like cutaneous lesions scattered over the body

A 15 year old boy, reported by Falbe Hansen (176), had exacerbations and remissions of stomatitis for one year before the hemogram revealed granulocytic leukemia He died of a hemorrhagic diathesis and autopsy disclosed granulocytic leukemia They believed that stomatitis of long duration, and the only symptom of leukemia, was extremely rare

Masons (435) patient, a 60 year old man, had marked gingival hypertrophy A 25 year old woman, reported by Cupar (135), had a rapidly progressive symmetrical hypertrophy of the gums during the fifth month of pregnancy She

died during a premature delivery and autopsy revealed granulocytic leukemia with granulocytic infiltration of the gums

The 37 year old man reported by E C Smith (639) had enlargement of both tonsils which were soft and necrotic The left tonsil was also ulcerated and partially purulent tissue replaced the anterior pillar of the fauces which extended anteriorly over the base of the tongue and was firmly fixed to the wall of the cheek This case was described as one of cancrum oris as a terminal manifestation of granulocytic leukemia Gillespie and Walker (225) described a 36 year old man who had severe granulocytic leukemia with acute tonsillitis complicated by peritonsillar abscesses He died following tonsillectomy and autopsy disclosed granulocytic leukemia

By far the most common nonspecific lesions according to Forkner (192b) are the bleeding diathesis Petechiae and spontaneous bleeding from the uninjured gingival and nasal mucous membranes occur in both acute and chronic leukemia but are much more frequent in the acute forms and in the terminal stages of chronic leukemia The decrease in the number of blood platelets explains at least in part these phenomena which may be seen in any form of thrombocytopenic purpura Increased tendency to bleed as the result of what is ordinarily inconsequential trauma (such as brushing of the teeth or blowing the nose) is noted frequently not only in patients having thrombocytopenia but also in patients having normal or increased numbers of blood platelets These symptoms of either spontaneous bleeding or bleeding as the result of minor trauma often are the initial symptoms which cause patients who have leukemia particularly the acute form to seek professional advice Because of the nature of the complaint a large majority of such patients first consult their dentists Frequently the seriousness of the situation is not appreciated and extraction of one or more teeth is performed Uncontrollable hemorrhage frequently followed by ulceration and in some cases osteomyelitis of the jaw then occurs

Favreul and Landais (181) Pollosson and Lebeuf (534)

and others have described noma occurring in patients with acute leukemia

Ulceration of the mucous membrane in patients who have leukemia particularly in the terminal stage of the disease, is a frequent occurrence according to Forkner (192b) Undoubtedly in some cases the ulceration is dependent upon an underlying involvement of the tissues with leukemic infiltrations, whereas in other cases it may depend primarily upon invasion of the mucous membranes by spirochetes and pyogenic organisms in individuals who have a lowered resistance to infection At times such processes lead to the diagnosis of Ludwigs angina diphtheria agranulocytic angina or scurvy, and the ultimate diagnosis is made only after the demonstration of the leukemic nature of the disease Not enough attention has been directed to the study of this similarity in disease pictures of acute leukemia and other diseases according to Forkner This criticism is still pertinent because the literature is filled with reports of cases thought to be agranulocytic angina which on more careful inspection were undoubtedly examples of acute leukemia in a "subleukemic" stage The instances [illegible] ocesses have [illegible] In some of [illegible] ls has been demonstrated

A patient reported by Marx (434) had chronic lymphocytic leukemia leukemic cutaneous lesions and smooth reddish thickening without ulceration of the uvula epiglottis and



Figure 144 Glossitis (iron deficiency) associated with chronic lymphocytic leukemia

pharynx Lindemann (392), Landais (368), Philip (520), Laugier (371), and Emile-Weil and Isch-Wall (165b), are among those who have reviewed the literature and reported cases illustrative of the clinical aspects of involvement of the oral cavity in leukemia

Cytopenia. Cytopenia, such as anemia, leukopenia and thrombopenia, may occur in association with the various types of leukemia The anemia may be associated with an iron de-

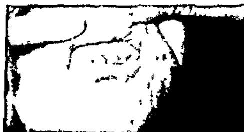


Figure 145 Agranulocytic membrane in a patient with chronic lymphocytic leukemia

ficiency and may result in glossitis When marked leukopenia occurs, an agranulocytic membrane may appear on the gums and thrombocytopenia may cause severe hemorrhage of the oral cavity

XI

MIKULICZ'S DISEASE

M.

though Mikulicz's disease may occur with various other conditions, it is probably most frequently associated with lymphosarcoma, in which the lacrimal and salivary gland involvement is a local manifestation of the general disease process

Some investigators believe that Mikulicz's disease progresses through an "aleukemic" stage to leukemia However, this theory has not been substantiated

In 1874, 14 years before Mikulicz described this disease entity, Gallasch (208a) reported a patient who had symmetrical enlargement of the lacrimal glands associated with leukemia. Although this patient had the usual histologic findings present in lymphocytic leukemia, the case was reported because of the unusual localization in the lacrimal glands

Among 10 patients with Mikulicz's disease, Schaffer and Jacobsen (600) found that four had lymphocytic leukemia Among these patients, three children had the acute form and one adult had chronic leukemia All of these patients died within two to eight weeks following examination In addition to Mikulicz's disease, one of these patients had numerous cutaneous petechiae of "variable age" Radding (543) found 23 case reports of Mikulicz's disease due to leukemic infiltration and described an additional case This patient was a "young" man who had chronic "aleukemic" lymphocytic leukemia Because of severe dyspnea and pulmonary infiltrations, "spray"

roentgenotherapy (600 r) was administered to the mediastinum and transfusions of whole blood were given This therapy resulted in "considerable improvement" However, the lacrimal and salivary glands continued to increase in size and became markedly painful, while the peripheral white blood cells decreased to 500 per cu mm He was then given a total of 600 r high voltage roentgenotherapy over the parotid glands which resulted in a "dramatic change" in his condition The lacrimal and salivary glands decreased to normal size and further roentgenotherapy caused regression in size of the axillary lymph nodes and spleen Jaffe (341f) presented a 48 year old woman with chronic lymphocytic leukemia who had a diffuse, firm, subcutaneous lesion which caused bilateral swelling of the neck and jaw This lesion was adherent to the underlying tissues but not to the skin, and the involved area was not tender She also had several firm, discrete nodules in the neck, below the mastoid process, and in the groin On examination, she presented bilateral swelling of the parotid and submaxillary regions, particularly on the left side Jaffe believed that the facial appearance was "characteristic of what is called Mikulicz's disease

The patient reported by Rowe (586) was a 55 year old woman who had chronic lymphocytic leukemia Bilateral, painless, nontender nodules appeared over the eyes and beneath the rami of the mandible She also had edema of the conjunctivae cervical, axillary and inguinal lymphadenopathy, and marked hepatosplenomegaly Labbe *et al* (365b) also described patients who had lymphocytic leukemia associated with marked leukemic infiltration of the lacrimal and salivary glands The patient reported by Haeckel (250) had enlargement of the lacrimal and parotid glands and the submaxillary lymph nodes There were painful tense and warm, "bean" sized cutaneous tumors scattered over the head and back There were numerous firm reddish wheals on the breast and a few on the back and abdomen Histologic examination of the cutaneous lesions disclosed round cell infiltration around the sebaceous glands and newly formed connective

tissue around these islands He died of "ulcerative enteritis" Because of the cutaneous infiltrations, fever, and splenomegaly, as well as the clinical course of the disease and the histologic picture of the tissue, the diagnosis was believed to be "aleukemic" leukemia Hurd (285) presented a 73 year old man who had symmetrical enlargement of all salivary and both lacrimal glands There was also generalized superficial lymphadenopathy, and enlarged mediastinal lymph nodes were demonstrated by roentgenograms Although the total white blood cell count was normal, this patient presented many features of chronic lymphocytic leukemia, including lymphocytic infiltration of the sternal bone marrow Feit (182b) reported a 21 year old woman who had "aleukemic" leukemia and involvement of the lacrimal and parotid glands, as well as submental, submaxillary, axillary and inguinal lymphadenopathy, and nodular infiltrations in the subcutis There was an irregularly outlined, 8 by 5 mm, hard, painless lesion on the back of the right hand which was covered with smooth, pseudoatrophic skin The histologic examination of this lesion revealed round cell infiltration of the corium (presumably lymphocytic) and polymorphonuclears and eosinophils There was a massive infiltration of lymphocytes and large epitheloid cells, with some evidence of necrosis and polymorphonuclear infiltration in these areas The patient reported by Owen and Hennessey (497) [illegible]
of the axill [illegible]
lymph node [illegible]
were "considerably enlarged and the lacrimal glands were the size of "tangerines There were similar leukemic deposits in the left bulbar conjunctiva in the lips, cheeks and hard palate The peripheral blood count revealed 11,000 to 22,400 white blood cells per cu mm, with 60 to 77 per cent lymphocytes

Three patients who had Mikulicz's disease associated with leukemia were reported by Leucutia and Price (383) The first patient was a 49 year old man who had "aleukemic" leukemia associated with symmetrical involvement of the lacrimal, parotid, submaxillary and sublingual glands The primary

manifestations appeared to have occurred in the lymphatic system and lacrimal and salivary gland enlargement apparently developed later Their second patient was a 57 year old woman whose first symptom was a swelling over the right eye, and later diarrhea Splenomegaly developed and a diagnosis of leukemia was made The lacrimal and salivary glands subsequently became enlarged The third patient was a three year old boy who first had cervical lymphadenopathy Six months later swelling of the face and marked "dryness" of the mouth occurred There was also enlargement of the lacrimal and salivary glands and the diagnosis was "subacute" lymphocytic leukemia

In reviewing the literature, Howard (297) and Schaffer and Jacobsen (600) found that many cases described as 'pseudoleukemia" should have been classified as true leukemia In many cases careful hematologic studies were not performed for a sufficient period of time to permit a correct diagnosis The reported cases which Howard believed exemplified this belief were those described by Brunn (79), Battle (32), Stock (655), Moorhead (460) and Paton (506) He believed these cases to be chronic lymphocytic leukemia from the onset, although they were "aleukemic at the time of examination Cases of lymphocytic leukemia associated with Mikulicz's disease have also been described by Hempelmann (275) and Griffith (243)

Histologically, the salivary and lacrimal glands are infiltrated and the parenchyma is replaced with lymphocytic cells There is, as yet, no explanation for the fact that only one case of Mikulicz s disease associated with granulocytic leukemia has been reported (Hennema 276) This patient had involvement of the salivary and lacrimal glands

XII

LEUKEMIA ASSOCIATED WITH OTHER DISEASES

A Mycotic Infections

1 Superficial Mycotic Infections Two patients who had leukemia associated with widespread cutaneous involvement with trichophyton rubrum were described by G M Lewis *et al* (388) One patient had lymphocytic, and the other monocytic leukemia The generalization of the cutaneous mycosis was considered to be related in part at least to the underlying disease process They were of the opinion that the systemic disorder lowered the resistance of the host sufficiently to predispose to the more active invasion of the mycotic agent A patient who had lymphocytic leukemia associated with a generalized epidermophyton inguinale infection was reported by Garb and Franks (211)

Bernard *et al* (42) called attention to the fact that serious complications due to candida albicans may occur following therapy with broad spectrum antibiotics for leukemia They noted that markedly severe thrush may develop Among their patients three had "acute" leukemia two lymphocytic leukemia and one granulocytic leukemia

2 *Deep Mycotic Infections* Cawley and Curtis (107) pointed out that the reticuloendothelial system is involved in both histoplasmosis and the leukemia lymphoma group of diseases It was their opinion that this group of diseases might predispose to histoplasmosis They cited four instances of the coincidental occurrence of these two rare diseases in a



Figure 146 Trichophyton rubrum infection in a patient with chronic lymphocytic leukemia

series of 88 cases of histoplasmosis and they believed that this incidence was greater than could be accounted for by mere chance Two cases of leukemia associated with histoplasmosis reviewed by Curtis and Cawley were reported by Riehl Jr (562a) and Williams and Cromartie (733) Riehl Jr described his case in 1925 This patient had a cutaneous eruption which appeared at intervals for seven years before admittance to the hospital Gastrointestinal disturbances including obstipation and tympanites subsequently occurred On examination there were widespread efflorescences consisting of discrete and confluent brown to violet colored papules and nodules of various sizes There were plum sized submaxillary and inguinal lymph nodes hepatosplenomegaly and evidence of consolidation at the base of the left lung There were 8 000 to 24 000 peripheral white blood cells per cu mm with many abnormal forms and the red blood cells numbered about 3 000 000 per cu mm Urinalysis disclosed albuminuria The clinical diagnoses of leukemia and leukemic metaplasia of the pleura and kidneys were made but the exact nature of the cutaneous eruption remained in

doubt The larger nodules on the chest became ulcerated before death which occurred three months after entrance to the hospital At autopsy, the bone marrow was greyish red in color, there was marked hepatosplenomegaly, verrucous endocarditis and multiple, firm, indurated cutaneous lesions Histologic examination revealed large cells, each containing numerous small round bodies surrounded by a capsule, in many of the cutaneous lesions Riehl noted a resemblance to leishmaniasis but interpreted the findings as an example of blastomycosis of the type described by Buschke In addition, there was a dense round cell infiltrate of the middle corium and about some of the blood vessels He was of the opinion that leukemia may have predisposed to the fungous infection The second case was described by Williams and Cromartie in 1940 This 56 year old man first had lymphadenopathy, two years previously, which was followed by loss of weight, shortness of breath, edema of the ankles, occasional fever, and sore throat There was marked enlargement of all palpable lymph nodes, redness and ulceration of the pharynx, pulmonary lesions and hepatosplenomegaly The hemogram disclosed 3 820 000 red blood cells per cu mm, 11 6 grams hemoglobin and 71 per cent "adult type" lymphocytes The clinical impression was "some form of malignant lymphoma" He died seven days after admission to the hospital and histologic studies at autopsy revealed H capsulatum in the lymph nodes, in the submucosa underlying the pharyngeal ulcers and in the epiglottis There was also evidence of chronic lymphocytic leukemia in the lymph nodes spleen liver, bone marrow, adrenal glands and kidneys They believed that chronic lymphocytic leukemia was the primary disease and the H capsulatum infection was coincidental

Raftery (544) reported the association of histoplasmosis and lymphocytic leukemia in a child Curtis (136) described a woman who had granulocytic leukemia Irregularly shaped ulcerated lesions then developed on the face and lips, as well as a lesion on the forehead which appeared to be a "large acne pustule" A pure culture of torula histolytica was ob-

tained from the acneiform lesion. Curtis commented that F. Mallory (422) had stated that practically every case of torula histolytica he had observed had been associated with "lymphoblastoma."

B. Carcinoma

Beck (39a) found that leukemia frequently occurs in association with other malignant diseases and a relationship between these conditions has been suggested. However, *among 289 cases of leukemia, he found only one case with* coexistent basal cell carcinoma (another previously unreported case is described in this section). Although there are numerous reports of infectious diseases as a predisposing cause of leukemia, he found only three reported cases associated with leukemia and one with a chancroid. However, he did not believe there was any relationship between these diseases and the leukemia. In the case of chancroid reported by Szodoray and Borza (672), a lymphatic tumor developed in the area which had been involved by the chancroid.

The association of malignant disease with chronic lymphocytic leukemia has been noted by many investigators and has given rise to some discussion as to its significance. The first authentic case of the simultaneous occurrence of malignant disease and leukemia was described by Whipham (724) in 1878. Bousser and Mathe (69b) discussed the problem based on personal observations of four cases and 90 additional reported cases. They pointed out that the development of epithelial tumors during the course of lymphocytic leukemia is not negligible. They found 29 cases of cutaneous carcinoma associated with leukemia. Fuhs (205), Schueffler (611) and Winer (735) reported unusual cases in which epithelioma of the skin developed from a leukemic infiltration. Linke (393) called attention to leukemoid blood reactions in carcinoma which, he stated, may be produced by (1) carcinoma products which stimulate the bone marrow or render it allergic, (2) hemorrhage, inflammation and necrosis of the carcinoma,

(3) irritation of the bone marrow by metastases (4) bone marrow carcinosis with myelophthisis and extramedullary blood formation

A patient with chronic granulocytic leukemia who presented melanosarcoma of the skin was reported by Horvath (296) One year after the appearance of these lesions metastatic nodules developed in the lungs and skin Horvath suggested that these pigmented nevi may have resulted from the generalized roentgenotherapy administered for the leukemia

Daron and Pizzolato (142) reported a 54 year old Negro who had giant cell carcinoma of the thyroid gland associated with acute granulocytic leukemia Six weeks previously a daily fever had suddenly developed as well as migratory polyarthritis dyspnea weakness and cough The hemogram disclosed 1 770 000 red cells and 104 000 white blood cells per cu mm with 49 per cent myeloblasts At autopsy the sternal bone marrow examination revealed hyperplasia of very immature cells which were mainly myeloblasts There was a firm yellowish white well circumscribed 2 cm nodule which in [illegible] nma [illegible] well [illegible] contained a variable amount of reticulated pink cytoplasm This carcinoma had invaded skeletal muscle and metastasized to a hilar lymph node Daron and Pizzolato believed the simultaneous occurrence of these two highly malignant diseases to be very rare

Case Report A 53 year old man first noted weakness and loss of weight five years previously, at which time the hemogram and histologic examination of a cervical node showed lymphocytic leukemia He was given roentgenotherapy but cervical axillary and inguinal lymphadenopathy as well as transient pains over the spleen had continued to be annoying symptoms He had received radium therapy for carcinoma of the lower lip "some years" previously and dyspnea had been present for the past year During the past month he

had petechiae and ecchymoses, some of which hemorrhaged, as well as bleeding from the mouth and nose, and soreness of the gums. On examination there was axillary, cervical and inguinal lymphadenopathy and hepatomegaly. There were 70,000 peripheral white blood cells per cu mm. The skin showed a lemon yellow pallor and there were many scattered, 2 to 4 cm, ecchymotic lesions in various stages of development present on the extremities and trunk and there were bleeding points in some areas. During the next three weeks, preceding death, the petechiae regressed but hematomas developed on the left hand and on the right side of the calf and blood oozed from the gums and nasal mucosa. At autopsy there was an 0.5 by 1.0 cm ulcerated lesion on the dorsum of the left hand which had a necrotic center surrounded by numerous small white abscesses. The anatomical diagnoses were chronic lymphocytic leukemia, bilateral passive congestion of the lungs, ulcer of the left hand and bilateral bronchopneumonia. Histologic examination revealed lymphocytic leukemic infiltration of the spleen, liver, lymph nodes, kidneys and skin.

Case Report. A 49 year old man, who was known to have chronic lymphocytic leukemia, had moderate superficial lymphadenopathy and residuum of phlebitis of the lower left leg which occasionally became swollen. On examination he had a persistent crusting lesion on the left preauricular area which had been present for three months. A scaly patch had involved the region above the right eyebrow for one year and a similar lesion had appeared on the right side of the nose. There was a crusted 5 mm. pearly bordered lesion in front of the right ear which was surrounded by a 1 cm. area of erythema, as well as two slightly raised, 'rough,' noninflammatory, 5 mm. lesions over the right eyebrow and on the right side of the nose. Histologic examination of the lesion in the left preauricular region

disclosed small aggregations of elongated, moderately hyperchromatic cells in the corium These cells formed small nests in rather dense connective tissue The diagnosis was basal cell carcinoma The lesions on the right side of the forehead and nose were found to be keratoses He died two months later and the anatomic and histologic diagnoses at autopsy were lymphocytic leukemia, marked secondary anemia fatty infiltration of the liver, edema and congestion of the lungs, myocardial degeneration and coronary sclerosis with healed infarction

C. Tuberculosis

There are many instances of the association of tuberculosis and leukemia It is the consensus of opinion among many investigators that leukemia lowers the resistance of the patient, thus activating a latent tuberculosis Also, involvement of the reticuloendothelial system by the leukemic process may affect the antibody system causing a diminution of antibodies, thus allowing the tubercle bacilli to gain a foothold (see Chapter IV)

Reviews of the literature and discussions of this relationship are contained in publications by J E Farber and Bylebyl (177), Jaffe (314d), and Ulrich and Parks (693)

D. Hodgkin's Disease

Leukemia associated with Hodgkin's disease has been mentioned by some investigators Willis (734) stated that it is not an infrequent occurrence However, among the cases we have observed and those reported in the literature this opinion appears to be incorrect A discussion of the association and relationship of these two diseases was presented by Seife *et al* (621)

E. Kaposi's Sarcoma

The relationship between leukemia and Kaposi's sarcoma was discussed in a previous monograph, KAPOSI S SARCOMA (Bluefarb, Springfield, Charles C Thomas, 1957)

F. Syphilis

Nanta (470b) described two patients who had syphilis and lymphocytic leukemia The first patient had primary syphilis Subsequently angina with cervical lymphadenopathy developed This lymphadenopathy never completely subsided but gradually became hypertrophic Twelve years later the peripheral blood picture was characteristic of lymphocytic leukemia The second patient, who had a syphilitic hemiplegia, was also found to have lymphocytic leukemia The patient reported by Barns and Rosenheim (29) was a "middle aged" woman who had tertiary syphilis The hemogram first suggested pernicious anemia but the typical picture of chronic granulocytic leukemia was later apparent The diagnosis of leukemia was confirmed at autopsy

Cannon's (97c) patient was a 34 year old man who presented an ulcerated lesion on the penis, grouped papular lesions on the trunk, face, and extremities, including the palms and soles, and superficial lymphadenopathy There was a "dime" sized, bluish red, eroded plaque on the left breast near the nipple, which was slightly thickened and firm on pressure The right tonsil and surrounding tissues were markedly swollen, dark red in color, with a sloughing ulcer The blood serologic reaction (Wassermann) was strongly positive and dark field examinations revealed treponema pallidum Following therapy with old arsphenamine, all the lesions disappeared except the one on the left breast, the papules in the right supraclavicular region and the ulcer of the tonsil The lymphadenopathy persisted Blood studies revealed chronic lymphocytic leukemia There were 60,000 white blood cells per cu mm, with 78 per cent lymphocytes and 11 per cent lymphoblasts

G. Urticaria Pigmentosa

The association of this condition with leukemia is discussed in another monograph in this series (Mastocytosis Volume II)

II Scleroderma

Kusunoki and Kuwabara (362) described a 48 year old man who had scleroderma associated with granulocytic leukemia He showed improvement of both the leukemia and scleroderma following parathyroidectomy

XIII

PROGNOSIS

In chronic leukemia, palliation of symptoms may be obtained by means of various therapeutic measures, but there is little evidence that such palliation greatly prolongs the life expectancy of any individual There are occasional patients with chronic leukemia who for various reasons, have been unable to receive definitive treatment but who nevertheless, have lived for relatively long periods with remarkably few symptoms Such instances obviously must represent simple variations in the natural history of these disease processes Individuals with chronic lymphocytic leukemia, who are in the older age group, and who do not have significant lymphadenopathy or anemia, usually do well without any type of therapy A patient who survived for 29 years with chronic lymphocytic leukemia was described by Marlow and Bartlett (432) With leukemia coming more and more into the 'limelight, particularly with the growing knowledge of cellular biochemistry, the picture for the future will likely be brighter It is to be hoped that some substances may be found that will be of much greater value in the control of chronic leukemia than are those that are available at this time (Watkins 710a)

It was noted by Leavell (375) that the duration of life after the onset of symptoms in nine patients with chronic lymphocytic leukemia who had specific cutaneous lesions did not differ from those who did not have these lesions

Specific cutaneous lesions appear late in the course of the disease when the life expectancy is commonly measured in

weeks, according to Goldhamer and Barney (231) Among the reported cases, they found that the time between the onset of specific cutaneous lesions and death varied from 11 days to four months an average of 64 days Sturgis (662a) was also of the opinion that cutaneous lesions occur late in the course of the disease and, following their appearance, the life expectancy can be "measured in weeks"

Emile Weil and Isch Wall (165a) believed that specific cutaneous lesions preceding an acute exacerbation of granulocytic leukemia was an important prognostic sign since the life expectancy was then only a "few months" Hollander *et al* (292) also believed the life expectancy, following the appearance of specific cutaneous lesions to be relatively short Their patient declined rapidly and progressively following the development of nodular cutaneous lesions which preceded the terminal acute stage of granulocytic leukemia

The total number of basophils occurring in the peripheral blood of patients with granulocytic leukemia were studied by Holmgren and Wohlfart (294) They concluded that the total number of basophils appears to be of diagnostic and prognostic significance The basophils are usually increased in number in granulocytic leukemia and a differential count of four to five per cent is "almost pathognomonic" of granulocytic leukemia

XIV

TREATMENT

Chronic Leukemia

THE PRESENT DAY treatment for leukemia usually consists of specific and nonspecific forms of therapy The nonspecific therapy consists of transfusions of whole blood, and the administration of vitamins, nutrients, antibiotics, hormones, antihemorrhagic agents, sedatives, and any other drugs which may be indicated for symptomatic or clinical improvement The specific measures include irradiation and the administration of hormones and chemotherapeutic measures

No curative method of treatment has been developed for any type of leukemia up to the present time However, therapy should be attempted in all cases because the remissions obtained by judicious selection and use of available chemotherapeutic agents have been well demonstrated It should be remembered that all available therapeutic agents are destructive primarily to the small lymphocyte and, to a lesser extent, to the erythroblast, myelocyte, granulocyte and megakaryocyte, but not to the reticulum cells which are the basic stem cell in all hematopoietic diseases (Block and Jacobson 55a) It should be remembered that the antileukemic drugs used today will not find a permanent place in the treatment of this disease

Nonspecific Therapy Transfusions of whole blood may be indicated when a progressive anemia develops in the course of chronic leukemia These transfusions are indicated when the peripheral red blood cells number less than 2,500,000 per

cu mm, the white blood cells less than 2,500 per cu mm, or the platelet level is less than 100,000

Antibiotics, such as Panmycin®, penicillin streptomycin or Terramycin®, are indicated specifically when infections are associated with leukemia or to prevent secondary infections

Antihemorrhagic agents, such as vitamin K, Protamine® and toluidine blue, are indicated when specifically required

Splenectomy is rarely of benefit in leukemia, although occasionally it is indicated in the presence of hypersplenism

Diet is of importance because a well nourished patient is less susceptible to the depressant effect of the various therapeutic agents upon hematopoiesis (Block and Jacobson 55a) Furthermore, an adequate diet is essential to the formation of antibodies and resistance to infection in general

Specific Therapy The current spec [illegible]

consi [illegible]

For t [illegible]

the age of the patient, the cytological type of leukemia, its acuteness or chronicity, the degree of organ infiltration, and the state of the bone marrow productivity should be considered (159)

With all the agents used in the treatment of leukemia the margin between the therapeutic dose and the toxic dose is small and careful clinical management is essential

Therapeutic response is classified as a complete or partial hematologic remission or a clinical remission only A complete hematologic remission can be obtained only when the peripheral blood findings for hemoglobin erythrocytes, leukocytes and platelets return to normal levels and the bone marrow findings revert to normal A clinical remission invariably occurs if there is a complete hematologic remission In the [illegible]

[illegible] usually present, although less prolonged In the remission classified as clinical only, subjective and objective improvement occurs, with a

gain in weight, subsiding of fever, improvement in appetite, and a sense of "well being" Regression of the hepatomegaly, splenomegaly and lymphadenopathy also occurs but without a satisfactory improvement in the bone marrow (159)

Chronic Lymphocytic Leukemia

Occasionally, chronic lymphocytic leukemia may run a slow and protracted course and no therapy may be necessary for years In most patients, however, therapy is indicated

Irradiation Therapy Local irradiation of the spleen liver and lymph nodes is, in most instances, the treatment of choice for patients having early chronic lymphocytic leukemia Total body irradiation and the oral administration of radioactive phosphorus have also been shown to be of benefit However, the chief hazards of irradiation therapy are the possible development of thrombocytopenia, progressive anemia or neutropenia

Triethylene Melamine (TEM) and Nitrogen Mustard. Karnofsky *et al* (329) first reported the clinical use of triethylene melamine in 1951 Triethylene melamine is quite often effective as a chemotherapeutic agent for chronic lymphocytic leukemia TEM is a powerful depressant of bone marrow function and can produce severe pancytopenia TEM is administered orally, usually before breakfast The dose is 2 5 mg a day, although 5 mg may be given in a single day The dose is administered over two successive days followed by an interval of two to four weeks during which no TEM is given

Dermatitis due to triethylene melamine therapy was reported by Frumin and Rubenstone (204) The dermatitis was maculopapular confined primarily to the upper extremities, and was associated with marked pruritus

The nitrogen mustard used most widely today is methyl bis (P chlorethyl) amine hydrochloride This drug is irritating to tissues and must be administered intravenously The usual course totals 0 4 mg /kg body weight and can be given in one or two doses The powdered nitrogen mustard is mixed with its diluent and immediately injected into the rubber tubing

of the infusion set The drug is washed into the blood stream by a rapid flow of the infusion The main indications for the use of nitrogen mustard are resistance to roentgenotherapy and generalized involvement of the disease The usefulness of nitrogen mustard is limited by the tendency of the drug, in many instances, to produce a greater destructive effect on the normal bone elements than on the leukemic cells

Although chronic lymphocytic leukemia is the most protracted and benign type of leukemia, it can be, on occasion, the least responsive to therapy

Chlorambucil (CB 1348), an aromatic nitrogen mustard, was studied by Ultmann *et al* (694) Chlorambucil was administered orally in doses ranging from 5 to 30 mg daily for five to seven weeks, so that an average course totaled 350 mg The results were encouraging in chronic lymphocytic leukemia

Corticotropin or Cortisone. These drugs are useful in the management of chronic lymphocytic leukemia, particularly in the later stages of the disease when radioresistance and thrombocytopenia may have developed Cortisone is particularly valuable in controlling the acquired hemolytic anemia which is occasionally present in patients having chronic lymphocytic leukemia

Sulzberger *et al* (664) reported regression of lymphocytic leukemia cutis following ACTH therapy

Chronic Granulocytic Leukemia

Irradiation. Ionizing irradiation, either by the use of localized roentgen rays to the spleen, total body spray, or by the oral or intravenous administration of radioactive phosphorus is the most effective therapy yet developed for chronic granulocytic leukemia However, this treatment can be employed only in localities which have adequate facilities and personnel (Burchenal, 84a) Irradiation therapy is usually administered over the spleen in doses of 50 to 100 r daily alternating the anterior and posterior regions, until a total of between 300 and 600 r have been given (Craver, 130b)

Osgood (496b) reported very satisfactory results in the treatment of leukemia with the use of titrated regularly spaced total body irradiation He believed that most of the beneficial effect of such therapy is related to the fact that the leukemic process is kept under continuous control by these repeated small doses of irradiation

Radioactive phosphorus may be administered orally or intravenously in solution such as sodium radio phosphate (P 32) Radioactive phosphorus was first used for the treatment of chronic granulocytic leukemia by Lawrence *et al* (373c) The radioactive half life is 14 3 days Localization is found particularly in the active bone marrow other sites of leukemic infiltration and in the bone proper The dose is usually 1/10 mc for each kg of body weight Excellent remissions may be produced with this technic with little or no radiation sickness and has been shown to be approximately as effective as roentgenotherapy However Platt (526) warned that *serious consideration must be given to the path*ologic changes in the testes and ovaries of patients who are in the reproductive period of life Observation of these organs has confirmed the possibility that spermatogenesis and oogenesis may decrease or disappear with resulting sterility in young persons who are given radiophosphorus

Myleran (1,4 Dimethane Sulfonyloxybutane) (GT-41) Excellent remissions marked by a feeling of "well being decrease in the size of the liver and spleen rise and maintenance of the hemoglobin level and decrease in hemorrhagic manifestations have been reported to occur following the administration of this drug for chronic granulocytic leukemia The drug is administered orally in doses up to 6 mg daily for four to six weeks followed by smaller maintenance doses

G A Hyman and Gellhorn (304) treated 21 patients with Myleran® They reported that significant remissions for periods up to 48 months were obtained in 17 patients There was restoration of the total blood cell count to normal figures improvement in the hemoglobin concentration and disappearance of splenomegaly in nine patients However eight

patients showed less complete remissions in that maintenance therapy was required Four patients who had subacute or chronic forms of the disease were not benefitted by this treatment

Wintrobe *et al* (737d) stated that Myleran® has proved to be the most effective chemotherapeutic agent for the treatment of this disease

Urethane. Urethane (ethyl carbamate) also has been beneficial in the treatment of chronic granulocytic leukemia Good subjective improvement, with a decrease in the number of peripheral white blood cells, has been noted following the oral administration of 3 gm a day Maintenance doses are somewhat lower, averaging 0 5 to 1 5 gm daily This drug causes a certain amount of nausea and vomiting as well as drowsiness, which may limit the patient's ability to tolerate adequate amounts of the drug

Colchicine Derivatives (Demecolcin®, Colcemid®). Recent studies (Moeschlin *et al* 457, Bock and Gross 58 and Leonard and Wilkinson 380a) indicate that these drugs have a marked specific effect on granulocytic cells This may prove to be another effective drug, which may be administered orally, for the treatment of chronic granulocytic leukemia

Shanbrom and Kahn (759) reported a 36 year old man with chronic granulocytic leukemia who had marked cutaneous involvement These lesions did not show improvement following treatment with triethylene melamine or Myleran® but regressed markedly following Demecolcin® therapy Although this patient was in the terminal stage of the disease when Demecolcin was administered, other clinical symptoms, as well as the results of laboratory studies, showed a beneficial response to this treatment

Arsenic Arsenic, administered as Fowler's solution by mouth, is rarely used at the present time for the treatment of chronic granulocytic leukemia

Nitrogen Mustards and Triethylene Melamine. These drugs have limited value for the treatment of chronic granulocytic

leukemia and are discussed under the treatment of chronic lymphocytic leukemia

Summary of Treatment of Chronic Granulocytic Leukemia No therapeutic agent available at this time has proved to lengthen the actual survival time of patients with chronic granulocytic leukemia However, good clinical and hematologic remissions have been obtained and the patient's active and useful life definitely increased with these therapeutic measures Since many of these drugs may give rise to severe hematopoietic depression, it is essential that frequent hematologic studies be done and the dosage regulated accordingly

Chronic Monocytic Leukemia

Monocytic leukemia usually occurs in adults and runs an acute or subacute course None of the therapeutic agents available today will regularly influence this disease

Chronic monocytic leukemia of the Naegeli type responds like chronic granulocytic leukemia, although this response may be somewhat more variable Leukemic reticuloendotheliosis (Schilling type) responds to therapy much as chronic lymphocytic leukemia

XV

POLYCYTHEMIA VERA

Introduction

POLYCYTHEMIA VERA, or erythremia is due to an increased production of red blood cells resulting in an increase of these cells per unit of blood above the normal amount Thus, there is an increase in both the total blood volume and in the cell volume

Dameshek (139c) described polycythemia vera as a disease of unknown origin characterized by an excessive production of all the bone marrow elements (panmyelopathy), with resultant increase in erythrocyte, leukocyte and platelet counts (pancytosis) Almost all symptoms of this disease are due to the great increase in blood volume and circulating red cell mass In addition there is a tendency for the development of two opposing processes thrombosis and a hemorrhagic tendency Approximately one fourth of all patients with polycythemia vera have sclerosis of the bone marrow and myeloid metaplasia of the spleen

Etiology

The causes of polycythemia were listed by Makler and Zion (421) as

1. Polycythemia vera
2. Secondary polycythemia
   a. High altitude
   b. Poisoning by heavy metals or aniline dyes
   c. Pulmonary disease preventing adequate oxygenation

Ayerza's disease
Emphysema

d Cardiac anomalies with a right to left shunt
Tetrology of Fallot
Complex of Eisenmenger
Pulmonary artery stenosis with septal defect

e Pulmonary hemangioma

Determination of the total red cell mass is of value in the diagnosis of polycythemia only when it aids greatly in differentiating polycythemia vera from the symptomatic type, according to Haden (249a) In symptomatic polycythemia, the amount per kg is not significantly increased, even when there is a marked increase in the red blood cells per cu mm Haden believed that a diagnosis of this condition could not be made on an increased number of red blood cells per cu mm alone A definite increase in blood volume, always present in this disease, must also be demonstrated Haden (249b) classified polycythemia as follows

I SYMPTOMATIC POLYCYTHEMIA Increase in red blood cells without an increase in blood volume (erythrocytosis), or increased blood volume without increase in red cell mass due to primary over-production of erythrocytes to compensate for

a Low barometric pressure
b Impaired oxygenation of lungs due to
  1 By-passing of lungs by heart disease
  2 Decreased areating surface in lung disease
  3 Decreased blood flow
c Impaired capacity of blood to carry hemoglobin, as in carbon monoxide poisoning

II POLYCYTHEMIA VERA

a Symptomatic, from interference with oxygenation by
  1 Congenital heart disease
  2 Ayerza's disease
  3 Alteration of hemoglobin (as methemoglobinemia)
b Idiopathic, from unknown causes

Cutaneous alterations are among the most characteristic symptoms of this disease, according to Sturgis (662a), and the

diagnosis is frequently suggested by a single glance at the patient The skin color, a mixture of blue and red shades, gives the appearance which is designated as a "reddish blue cyanosis" In polycythemia vera the blood circulation is sluggish as a result of the greatly expanded vascular bed, increased blood volume, increased blood viscosity and increased number of formed elements in the blood The engorged capillaries and reduced rate of blood flow permit an accumulation of reduced hemoglobin which produces the reddish blue cyanosis of the skin However, from 10 to 15 per cent of these patients do not have cutaneous changes

Callender (92) suggested that polycythemia vera may be analogous to chronic leukemias He described the condition as

1 Increase in red corpuscles of the blood Platelets are increased and, especially in the later stages, there is an increase in granulocytes which might be considered as analogous to the appearance of considerable numbers of 'blasts' in granulocytic leukemia

2 The bone marrow shows erythropoietic hyperplasia The spleen is enlarged, usually with relatively little evidence of erythrogenesis The enlargement appears to be due to the increase in blood corpuscles in the red pulp

3 Reticulum of the organs involved shows no change

4 Irradiation is apparently of little benefit

The combination of erythremia and leukemia which occurred in several patients was believed by Parkes Weber and Bode (502e) to be one of the main arguments in favor of an excessive erythroblastic activity of the bone marrow as the cause of polycythemia vera Some investigators object to comparing erythremia with leukemia because only fully developed normal erythrocytes are present in the peripheral blood in erythremia, while immature leukocytes are characteristic of leukemia However, others do not agree with this belief since there are reports of rare cases of leukemia in which the increased leukocytes consisted mostly of mature neutrophils or eosinophilic polymorphonuclears Parkes-Weber and Bode re-

garded the neoplastic theory of the origin of myelemia, erythremia and the entire erythroleukemic group of diseases as the most acceptable one This neoplastic process may have the following forms· erythremia, erythroleukemia, erythremia followed by granulocytic leukemia, granulocytic leukemia followed by erythremia, and granulocytic leukemia

It was noted by Isaacs (308a) and Christian (113b) that the reddish cyanotic appearance is apparently not always directly associated with the increase in red blood cells Morris (461) described a patient with an erythremic erythremia whose red blood cell count was not increased Among 10 cases of polycythemia vera, Christian (113b) found that the deep coloration of the skin did not always occur The skin appeared to be pale in some cases, indicating that the depth of skin color is due, at least in part, to the location and stage of distention of the capillaries Several investigators have studied the capillaries, peripheral blood flow, cardiac output and utilization in this disease with regard to the cyanosis It appears that many of the symptoms and signs are due to a slowed capillary circulation of blood normally saturated with oxygen

Little is known of the actual factors which stimulate cell growth Loss of blood, either through hemorrhage or by excessive destruction (*hemolysis*), *appears to be a powerful* stimulatory factor to the bone marrow since the immediate reaction is an outpouring of early red blood cells (reticulocytes), granulocytes and platelets, according to Dameshek (139c) However, another stimulatory factor which affects only the red blood cells is anoxemia or arterial unsaturation Increased erythropoiesis results from high altitudes and from certain types of pulmonary or cardiac disease Although the increased erythropoiesis which occurs with hemorrhage, hemolysis or anoxemia is readily understood, the exact mechanisms by which such stimulation takes place is not known If, for example, hemolysis liberates a stimulating substance, Dameshek wondered how the results of hemorrhage in which blood is actually lost outside the circulation can be explained

Although little is known regarding stimulatory factors, even less is known of possible inhibitory factors, which he believed are probably also present "Were it not for such 'homeostatic' factors, bone marrow might conceivably develop out of all proportion to the needs of the body Certain indications are present implicating the spleen as a bone marrow 'regulator' or inhibitor, but actual proof of such substances in splenic extracts is thus far lacking We must conclude that although the bone marrow probably has normal stimulants and inhibitors which balance each other, resulting in extraordinarily stable blood counts, their nature is obscure'

In polycythemia vera according to Dameshek (139c), "all stops to blood production in the bone marrow seem to have been pulled" There are great numbers of nucleated red blood cells and granulocytes in all stages of maturation and megakaryocytes actively producing platelets in the bone marrow Because of their large number and their size, the megakaryocytes often dominate the marrow picture Dameshek speculated on the cause of this enormous productivity of the marrow Hemorrhage and hemolysis are not present, as mentioned by E B Miller *et al* (449) There is no evidence of anoxemia cyanosis is lacking, and the arterial saturation is normal Some investigators have stated that a local anoxemia affecting only the marrow might be present and have pointed to arteriosclerotic lesions in the marrow to support this view, as mentioned by Reznikoff *et al* (557b) However, Dameshek believed "This may well be a mistaken cause and effect relationship and the reverse might even be true, i e, the polycythemic state may lead to early arteriosclerosis" He believed a more important factor to be that anoxemia leads only to an increase in red blood cells and not to leukocytosis or thrombocytosis as mentioned by Loman and Dameshek (395) and Hurtado *et al* (302) "Fundamentally, the disease may be considered as a disorder of the bone marrow characterized by an excessive production of blood cells by the granulocytes and megakaryocytes To use Greek terms, there is panmyelopathy, which in turn results in pancytosis"

Dameshek also stated that "For whatever reason the disease is present, the panmyelopathy results in an enormous increase in blood cells All the elements are affected, with the result that the red blood cell count, the polymorphonuclear leukocytes and the platelets become increased Individual cases of polycythemia differ greatly, not only from the standpoint of how many blood cells are being produced but in the relationship of the three different marrow elements to each other For example, some cases show only a moderate elevation in erythrocytes, with, however, an extreme degree of thrombocytosis, while in others the leukocyte count may be at, or close to leukemic levels, with only slight increase in red blood cells and platelets" The most important end result of the extreme degree of panmyelopathy in polycythemia vera is the development of an enormous mass of red blood cells in the circulation, according to Dameshek The percentage volume of packed red blood cells (hematocrit) in relation to the total amount of blood becomes greatly increased and may reach levels of 60, 70 or even 80 per cent However, this increase in red blood cell concentration is, in itself, not sufficient to cope with the continued great production of red blood cells As a result, the total volume of blood becomes expanded to double or triple the normal values Parallel with this increased volume, the hematocrit continues to rise, so that finally the total red cell mass, which is normally about 45 per cent of 5,000 cc (2,250 cc), may become increased in some cases to 75 per cent of 15,000 cc (11,250 cc) or an amount of four or five times the normal

Pathology

The histologic picture of the cutaneous lesions which occur in polycythemia vera were described by Weidman and Klauder (715b) They found the outstanding feature to be round cell infiltration in the corium Although these cells appeared to be somewhat more dense around the blood vessels, they also occurred in large numbers in other areas and were abundantly and diffusely distributed in the collagenous

interspaces In the infiltrate they noted very few polymorphonuclears and the "overwhelmingly preponderant cell may be tentatively called a macrophage" With Graham's benzidine staining the oxydase granules became so abundant that the nucleus was completely obscured The blood vessels uniformly exhibited moderate swelling and hyperplasia of their adventitial and lining endothelial cells The walls of some of the larger vessels were edematous and a fibrous thrombus was present in some of the capillaries

Congestion of the buccal mucous membranes is common in all cases according to Naegeli (468), and the histologic changes in the mucous membranes show that all the smaller vessels are distended with blood and there is extravasation of blood into the tissues

Bone Marrow The sternal bone marrow of patients having polycythemia vera was studied by Block and Bethard (55b) On histologic examination they found that the marrow was densely cellular with a marked decrease in iron or an absence of iron granules and there were clumps of stem cells The differential count was fairly normal except for a "borderline high" erythroblastic percentage and prominent megakaryocytes This typical picture was observed in the bone marrow sections in about 80 per cent of the patients with polycythemia vera who were studied With bone marrow smears about 50 per cent of the patients showed an extremely cellular marrow with numerous megakaryocytes and very large clumps of platelets

The signs and symptoms of polycythemia vera were listed in order of frequency by Lawrence *et al* (373b)

		Per Cent
1	Headache	45
2	Dyspnea or orthopnea	34
3	Dizziness or vertigo	28
4	Ocular symptoms	27
5	Epigastric discomfort	25
6	Definite history or diagnosis of peptic ulcer	19
7	Precordial chest pain	16
8	Pruritus	14
9	Thrombophlebitis of the veins of leg or arm	13

		Per Cent
10	Cerebral thrombosis	10
11	Gout	7
12	a Coronary thrombosis	4
	b Thromboses, other than cerebral or coronary	4
	c Neoplasms	4

The symptoms and signs of polycythemia are varied At times routine examinations reveal erythrocytosis, although the patient is relatively asymptomatic, while others present ruddy cyanosis, headache, exertional dyspnea, pruritus or dizziness The diagnosis is sometimes made following focal symptoms in the nervous system or vascular accidents such as thrombophlebitis, visceral infections, or hemorrhage incidental to minor surgery Some patients do not appear to be plethoric, while other have the characteristic ruddy cyanosis The ocular fundi usually present increased venous filling, the veins are often engorged and of a dark color, while hemorrhages may be present, according to Stroebel and Law (661b) Papilledema, which rarely occurs, will regress when the erythrocyte hypervolemia is controlled

Stroebel and Law (661b) stated that splenomegaly occurs in 64 per cent of patients having the "simple" type of polycythemia vera, in 84 per cent of the cases characterized by mature leukocytosis, and in 90 per cent of those having the leukemoid type of the disease Although the nature of the splenomegaly is not always clear, they stated that in cases of "simple" and mature leukocyte type as well as some of the leukemoid type splenomegaly will regress following reduction of the blood volume by phlebotomy It was then presumed that a congestive type of splenomegaly had been present However, the splenomegaly will persist following phlebotomy in many of the leukemoid cases particularly when this organ is hard and markedly enlarged It is then presumed that the splenomegaly is due to myeloid metaplasia Hepatomegaly is difficult to evaluate, particularly in early and simple mature forms of the disease Among 240 cases, they found that cirrhosis occurred in one patient who had the leukemoid type They also reported hyperuricemia in 28 cases of the

simple type and in 54 per cent of those having myeloid im maturity There was clinical gout in 8 per cent of the simple type 15 per cent of the mature leukocytic type and in 46 per cent of the leukemoid type of polycythemia vera Duodenal ulcer was present in 15 per cent of the cases regardless of the type while its incidence in the general population is consid ered to be about 10 per cent Vascular accidents such as thrombosis or hemorrhage occurred frequently in these pa tients Stroebel *et al* (661a) found this to occur in 30 per cent of the patients prior to definitive therapy Among a group of patients having uncontrolled polycythemia vera as well as those in whom the cause of death was known there was some type of vasculur episode as the cause of death in 56 per cent of the cases They believed that increased throm bosis would be expected to occur because of the increased blood viscosity in uncontrolled polycythemia vera but the cause of hemorrhage was less apparent Various theories re garding this hemorrhage include dilated engorged small ves sels reduced oxygen tension at the capillary level and reduc- tion of fibrinogen in the blood

The Laboratory Findings

1 Elevated total red blood cell count (more than 6 000 000 cells per cu mm)
2 Elevated hemoglobin
3 Elevated total white blood cell count
4 Increase in number of polymorphonuclears
5 Elevated blood platelet count
6 Elevated blood volume
7 Elevated hematocrit
8 Distended capillaries
9 Elevated basal metabolic rate
10 Hyperuricemia
11 Red and white blood cell hyperplasia and megakaryo cytic hyperplasia of the sternal bone marrow

The peripheral blood cell count range in polycythemia vera was given by Dameshek (139c) as

Hemoglobin	100 to 160 per cent (15 6 to 25 0 gm)
Red blood cells	6,500,000 to 12,500,000 per cu mm
White blood cells	8 000 to 50,000 per cu mm
Platelets	1,000,000 to 6,000,000 per cu mm
Reticulocytes	1 to 6 per cent
Polymorphonuclears	75 to 90 per cent
Metamyelocytes	5 to 15 per cent
Myelocytes	0 to 5 per cent
Nucleated red blood cells	0 to 2 per cent
Hematocrit	55 to 80 per cent
Mean corpuscular volume	70 to 95 cu microns
Mean corpuscular diameter	7 0 to 7 5 microns

The differential clinical and laboratory features of polycythemia vera and secondary polycythemia were listed by Dameshek (139c) as

	Polycythemia Vera	*Anoxemic or Secondary Polycythemia*	
Fundamental State	Hyperplastic panmyelopathy	Anoxemia	
Etiology	Unknown	Anoxemia	Altitude Cardiac Pulmonary
Clinical	Plethoric appearance no pulmonary abnormalities splenomegaly and hepatomegaly, no clubbing of fingers	Cyanosis chronic pulmonary or congenital cardiac abnormality (cor pulmonale) except in altitude sickness no splenomegaly, clubbing of fingers	
Bone Marrow	Excessive erythroleukothrombocytopoiesis	Excessive erythropoiesis	
Blood	Pancytosis, erythrocytosis leukocytosis polymorphonuclears increased band forms increased thrombocytosis	No pancytosis, erythrocytosis white blood cells low or normal polymorphonuclears band forms and platelets normal	
Blood Volume	Very high	High	
Red Cell Volume	High	High	
Plasma Volume	Normal or increased	Low	

Arterial Oxygen
Saturation ...... Normal Diminished

Cutaneous Symptoms

The cutaneous symptoms of polycythemia vera may be explained on a circulatory basis and classified as (56b).

I Those types related to vascular distention and increased viscosity of the blood.
   a Purplish red color of the skin and mucous membranes
   b *Hemorrhages, ecchymoses, with resulting pigmentation*
   c Hemangioma, spider nevi
   d Scrotal (furrowed) tongue
   e Acne urticata, urticaria, rosacea
   f Pruritus, dry skin, eczema, and erythroderma

II Those types related to organic changes in the blood vessels
   a Thrombosis
   b Ulcerated nodules of the legs
   c Erythromelalgia
   d Scleroderma-like lesions

III Those related to heat and cold The symptoms become increased in severity in cold climate

I. Symptoms Related to Vascular Distention and Increased Viscosity of the Blood. It was shown by Brown and Giffin (76a) that the capillaries and venules of the skin have a storage function when under stress Their capacity for storage is provided by the distention and utilization of all the available capillaries of the skin The accommodation of the blood vessels to the increase of blood volume in polycythemia vera apparently occurs first in the vascular internal organs, the spleen, the liver, and in the large veins With progression of the disease and greater increase in blood volume, the peripheral veins, and eventually the venules and capillaries of the skin take part in the accommodation The distention of the

capillaries and venules is frequently extreme, which explains in part the changes in the color of the skin and mucous membranes so characteristic of the disease The capillaries can often be recognized macroscopically in the nail fold as fine red streaks

All patients show an increase in the total volume of the circulating blood The average for a series of cases studied by Brown and Giffin (76b) was 166 cc for each kilogram of body weight Engorgement of the skin capillaries disappears when the total volume of the blood is diminished to approximately 100 to 110 cc for each kilogram of body weight

The skin color is predominantly red (an erythrosis) and this redness is more marked on the facial and acral areas The color is described as resembling that of a chronic alcoholic or the color produced by blushing exposure to fire, or by silver nitrate inhalation, according to Harrop and Wintrobe (260b) Associated with the erythrosis, there are dilated superficial blood vessels (telangiectases)

The characteristic color rarely extends down further than the neck There is also involvement of the mucous membranes, the buccal mucosa, fauces, pharynx and tongue are frequently of a deep bluish color The color may vary from one patient to another and is not always the same in one patient Osler s classic remark that these patients may be "as red as a rose in summer" and indigo blue in winter," fixes this characteristic in mind This typical appearance is somewhat influenced by heat or cold It is intensified by cold and the shade becomes more reddish with warmth This can usually be demonstrated by placing the hands which have a blue color in warm water and rubbing them thus increasing the circulation and changing the color to red

In a group of 10 cases, Christian (113b) noted that the deep color was not always present Some patients appeared to be pale, indicating that the depth of color in the skin is due, at least in part, to the location and state of distention of the capillaries, according to Brown and Giffin (76c)

These patients do not have cyanosis according to Lunds



Figure 147 Polycythemia vera with erythema of the face and macroglossia (*Quart Bull Northwestern Univ M School* 29 8, 1955)

gaard and Van Slyke (406b) who found a normal oxygen saturation of the arterial blood However, they do become cyanosed very readily because of the increased hemoglobin content which magnifies the influence on capillary unsaturation, increased width and number of skin capillaries, and retardation of capillary flow due to increased viscosity and capillary distention

Bleeding from the gums and epistaxis are frequent and such hemorrhages may be produced by coughing or sneezing Lundsgaard (406a) believed the abnormal color of the skin and mucous membranes to be due to the accumulation of reduced hemoglobin in the blood which, in turn, is due to engorgement of the capillaries and the reduced rate of flow through these small branches of the vascular tree

Cutaneous hemorrhages are quite frequent in polycythemia vera according to Harrop and Wintrobe (260b), and purpura may result from the slightest trauma Zadek (748b) described a patient who presented extensive hemorrhage which soon spread to involve almost the entire skin, following the application of a mustard plaster

There is a marked tendency to bleed especially following operative procedures however simple There may be severe bleeding from the gums after dental extraction which necessitates packing and suturing A patient described by Dameshek and Henstell (139h) had severe bleeding with hematoma formation in the gluteal muscles following an intramuscular injection

Glazebrook (228) described a patient who had koilonychia during bursts of activity of the bone marrow The demand of the hyperplastic hemopoietic tissues for iron during such active phases may be excessive and the serum iron was found to be low Generalized roentgenotherapy reduced the peripheral blood count considerably and resulted in a marked increase in the serum iron content No doubt this release of iron enabled the nail dystrophy to heal

Clubbed fingers are usually not present in true polycythemia but may be present in the familial type and in erythrocytosis secondary to lesions of the heart and lungs

The superficial appearance of the eyeballs is often striking according to Harrop and Wintrobe (260b) They may appear "blood shot" or there may be only a few scattered dilated venules The conjunctivae of the lids are often intensely red suggesting inflammation

Generalized purpuric eruptions widespread petechial hemorrhages and telangiectases on the face which simulate the appearance in cirrhosis of the liver have been reported Extensive subcutaneous hemorrhages and purpura may follow the application of poultices and heat

Pigmentation of the skin is considered to be the result of persistent hyperemia of the skin in some cases In cases of long duration brownish pigmentation results from small cutaneous hemorrhages (*hemosiderosis*) *Many of these* cases simulate Majocchi s disease (purpura annularis telangiectodes)

Bluefarb *et al* (56f) presented a 60 year old woman who had hemosiderosis stasis dermatitis and polycythemia vera She had dyspnea palpitation orthopnea and edema of the feet

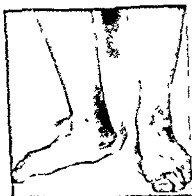


Figure 148 Hemosiderosis of the legs, associated with polycythemia vera (*Quart Bull Northwestern Univ M School,* 29 8, 1955)

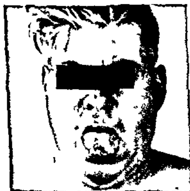


Figure 149 Cyanosis and macroglossia associated with polycythemia vera (*Quart Bull Northwestern Univ M School,* 29 8, 1955)

There is a marked tendency to bleed especially following operative procedures however simple There may be severe bleeding from the gums after dental extraction which necessitates packing and suturing A patient described by Dameshek and Henstell (139h) had severe bleeding with hematoma formation in the gluteal muscles following an intramuscular injection

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and legs for the previous 10 years and hypertension for five years, while an ulcer had been present on the right leg for one year Generalized pruritus and maculopapular cutaneous lesions had appeared three weeks before examination There was a stasis dermatitis, a 1 5 by 3 cm ulcer on the right leg and excoriated, papulovesicular lesions on the legs, thighs and lower trunk Her pulse rate was 108 per minute, blood pressure 180/115 and the heart was enlarged to the left A small "mass" could be palpated in the upper left quadrant of the abdomen Biochemical studies revealed 48 mg /100 cc non protein nitrogen The hemogram disclosed 150 per cent hemoglobin, 9 020,000 red blood cells and 8,650 white blood cells per cu mm Following phlebotomy (two pints 946 2 cc) the hemogram showed 148 per cent hemoglobin 8,860,000 red blood cells and 8 000 white blood cells per cu mm

Hemangiomata and vascular nevi, especially spider nevi, are fairly frequent lesions in polycythemia vera Two of Ssutejev's (648) patients had disseminated pigmented areas of erythroderma, in addition to the characteristic redness of the face In other cases he described the skin of the face as "cherry red," the capillaries were enlarged and "disseminated dark red angioma like lesions resembling drops of dried cherry juice on a white sheet and brownish red pigmented macules" were present in this area

The tongue is usually large, thickly coated, beefy red in color and furrowed (scrotal tongue) Hypertrophy of the papillae results in a granular appearance

H W Smith (641) described the tongue as "larger than normal beefy red in color with furrows and fissuring which may be obvious on the surface" The vascular engorgement is very marked and some patients have had several hemorrhages after dental extraction or they are able to suck blood from the tongue

The color of the mucous membranes is usually described as a "deep raspberry red" or "like that of inflammation," as mentioned by Naegeli (468) Gaisbock (207) believed the marked difference of the color of the mucous membranes depended



Figure 151 Rosacea associated with polycythemia vera (*Quart Bull Northwestern Univ M School* 29 8 1955)

upon whether the underlying structures were hard or soft. Schreyer (610) described the histologic changes in the mucous membranes of the upper respiratory tract in two cases All of the smaller vessels were distended with blood, which had also extruded into the tissues Epistaxis and bleeding from the gums are common in polycythemia vera

McCarthy (411a) reported a 55 year old man who had generalized, small, red, papular lesions, which were somewhat pruritic, and large wheals There was a scaling pustular dermatitis on the right forearm Weidman and Klauder (715b) described the occurrence of wheals at the site of scratching

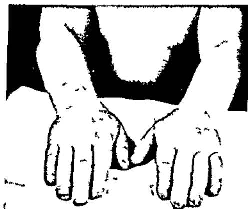


Figure 150 Eczematous dermatitis of the hands associated with polycythemia vera (*Quart Bull Northwestern Univ M School,* 29 8, 1955)

Kaposi (328b) used the term "acne urticata" to designate a chronic, severely pruritic cutaneous disease with lesions first appearing on the face and later on the extremities particularly on the extensor surfaces The cutaneous eruption is composed of pale red, elevated wheal like papules ranging from the size of a 'pea to that of a small coin' which have a vesicle, containing a turbid material, on the summit As a result of scratching, the vesicle or pustule soon disappears The surface of the papule becomes excoriated and crusted The lesions undergo involution with formation of a delicate scar and

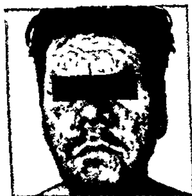


Figure 151 Rosacea associated with polycythemia vera (*Quart Bull Northwestern Univ M School*, 29 8, 1955)

pigmentation The eruption appears in crops accompanied by severe pruritis burning and pain The course of the disease is chronic lasting for months or years Kaposi s patients did not have polycythemia vera

Werther (722b) in 1922 was the first to describe such a case in association with polycythemia vera The patient was a 24 year old man whose peripheral red blood cell count was 8 000 000 per cu mm He had papules with a central vesicle or pustule on the face and neck as well as severe pruritus

The second case of this type was described by Pick and Kaznelson (523) This 48 year old man had small cutaneous nodules on the face for seven years The lesions later appeared on the scalp breast back and finally on the extremities They were most pronounced on the face where they first appeared as rose red urticarial papules but later became brownish red A vesicle or pustule appeared in the center followed by a crust The lesions regressed leaving either pigmentation or a slight scar There was occasional pruritus and pronounced vasomotor instability The only effective treatment was roentgenotherapy to the bone marrow This reduced the red blood cells from 8 000 000 to 3 000 000 per cu mm and the cutaneous lesions disappeared They suggested the name "acne urticata polycythemia"

A 63 year old man described by Richter (559a) was a questionable example of this condition His face was reddish blue in color with numerous telangiectases while inflammatory infiltrations the size of "lentils" were present around the nose

Mestschanskis (444) patient a 52 year old man had 8 000 000 peripheral red blood cells per cu mm and 116 per cent hemoglobin His face was bluish red in color and there were many bluish red "lentil to pea sized" papules on the scalp face neck, and breast Some of the lesions had a pustule in the center others were necrotic or scaly There were many isolated vesicles on the lobes of the ears On the penis scrotum and thighs there were numerous bluish red papules and pustules the papules were moderately infiltrated The

Roentgenotherapy caused a reduction of the red blood cell count and improvement of the cutaneous lesions This case is the only one recorded in which the test for oxydase granules in the infiltrating cells was done to determine whether these

to the region of the blood vessels in the subpapillary plexus, in the subcutis, and around the appendages In the first location, the vessels were extremely dilated and were described as "varicose" in some areas Arteries deep in the cutis showed endarteritis fibrosa with obstruction in some places Some were thrombosed and when this occurred, the cell and its environs were the seat of round cell infiltration and a slight increase of polymorphonuclears, although they were not as numerous as the monocytes The deep veins were markedly engorged and the surrounding stroma appeared vacuolated The vascular endothelium was swollen in some areas, where it bulged into the lumen The perivascular round cell infiltrate was usually only a delicate mantle, but occasionally there were nodular exaggerations The cells consisted of hyperplastic adventitial cells, a few polymorphonuclears, mostly neutrophilic, but occasionally eosinophilic There were oxydase-laden cells, of medium size with a strikingly small, round, dark nucleus, which was usually eccentric The cytoplasm was scanty and appeared to be of the same size as the plasmacytes The oxydase test, with naphthol blue as the reagent, was used, and the overwhelming majority of the infiltrating cells stained solidly blue He regarded the cells as descendants of the granulocytic series

Andrews (10b) reported a 45 year old man whose peripheral red blood cell count varied from 7,000,000 to 13,000,000 per cu mm His face and scalp were deep red in color and diffusely studded with papulopustules The shoulders and a triangular area on the chest presented intense erythema, with multiple papules and pustules The papulopustules had been present for six years, first appearing on the face and slowly

lesions were pruritic Histologic examination showed 'non specific inflammation"

Bohnstedt (61) described two cases The first patient, a 48 year old man, had a red blood cell count of 8,000,000 per cu mm and 135 per cent hemoglobin A diagnosis of polycythemia vera had been made five years before the cutaneous lesions appeared There were "pea sized" papules of intense "raspberry red" color, pustules, pigmented areas, and delicate scars which involved the face, neck, trunk and buttock The mucous membranes were of a deep red color and the entire skin appeared reddish The symptoms were moderate pruritus and pronounced dermographism Histologic examination of the papules showed "nonspecific inflammation" The second patient, a 56 year old man, had 12,000,000 red blood cells per cu mm and 150 per cent hemoglobin His face had been of a "red color" for many years Six months previously, isolated, "lentil and pea sized' nodules, which were intensely red and infiltrated, appeared on the face, back, breast, abdomen and scrotum The lesions on the face were of a "raspberry' color There were also pustules which regressed, leaving pigmentation and delicate scars The mucous membranes were red in color and the skin in general, particularly that of the face, was bluish red in color There was moderate pruritus and pronounced dermographism Rubbing of the involved areas produced an urticarial reaction with swelling of the papules Histologic examination showed nonspecific inflammation Bohnstedt noted the resemblance of the lesions on the face to those present in rosacea, although these lesions were of a more intense "raspberry color Moreover, they were not confined to the face and were accompanied by vasomotor instability

Gans (210b) described a 42 year old man whose peripheral red blood cell count was 9 500 000 per cu mm and the hemoglobin 124 per cent There was a 'palm sized," slightly raised, discrete and confluent lesion on the chest which was moderately inflamed and painful on pressure Delicate vascular branches were apparent on the surface Similar cutaneous tumors and nodules were irregularly scattered over the trunk

A patient described by Bluefarb (56b) was a 55 year old man who had precordial pain radiating to the arms, particularly the left, and pain in the left leg He also complained of vertigo, palpitation, a frontal headache which occurred daily, occasional edema of the ankles and a loss of 22 pounds in weight On examination he appeared to be plethoric. There were cardiac enlargement, precordial friction rub, some dullness, and diminished breath sounds and rales in the right lung The blood pressure was 116/84 The edge of the liver was tender and could be palpated six cms below the costal margin in the midclavicular line On palpation the spleen was firm, rounded and extended four cms below the costal margin He had an acneiform eruption with scratched papular lesions, about 2 cm in diameter, most marked on the back and right side of the trunk and diffusely scattered over the chest There were several spider nevi on the back The papular lesions had been present for two years and at the time of



Figure 152 Photomicrograph showing positive oxidase reaction of an acneiform papule in polycythemia vera (*Quart Bull Northwestern Univ M School*, 29 8, 1955)

spreading over the scalp, chest and back Histologic examination of a papulopustule from the chest showed only a non specific inflammatory reaction about the hair follicles and numerous polymorphonuclears

Rostenberg (581) reported a 52 year old man who had numerous dark red cutaneous lesions, of 'lentil to large pea size," on the trunk and extremities Some lesions showed definite wheals, while others were topped by an adherent crust or by small pustules Some lesions on the extremities had undergone involution, leaving superficial scars and pigmentation Many lesions on the trunk had been scratched and simulated neurotic excoriations

Costello (127a) described a 40 year old man with an eruption consisting of fine, discrete, pruritic papules on the face, sides of the neck, upper part of the back and anterior aspects of the shoulders and chest Weinmann (716) also described a patient who had acne urticata polycythemia

Weidman and Klauder (715b) reported a patient who had acne urticata associated with polycythemia vera They reviewed the literature regarding this association and concluded that *acne urticata may occur as a cutaneous manifestation* of polycythemia vera and, since it is analogous to a leukemid, it might be described as a "polycythemid" In describing the histologic picture of polycythemia vera, they stated that *the* outstanding feature is the round cell infiltration present in the corium Although these cells are somewhat more dense around the blood vessels, they are numerous in other areas as well, and abundantly and diffusely distributed in the collagenous interspaces Polymorphonuclears were practically absent in the infiltrate The overwhelmingly preponderant cell may be tentatively called a microphage ' they stated By *Graham's benzidine method oxydase granules* were brought out in such abundance as to completely obscure the nucleus The blood vessels uniformly exhibited moderate swelling and hyperplasia of their adventitial and lining endothelial cells The walls of some of the larger vessels were edematous and a fibrous thrombus was observed in some of the capillaries

established Pruritus may occur at any time during the day sometimes after eating or when the patient perspires but it is most frequent at night after retiring The pruritus is rarely spontaneous and is usually provoked by heat particularly bath water but it occasionally follows the use of cold water The pruritus may be localized or generalized depending upon the extent of bathing and usually involves the forearms thighs chest and back particularly between the scapulae The sensation is described as "burning" "tingling or "prickling" although only redness of the skin is evident on examination The pruritus usually disappears spontaneously in about 15 minutes but scratching may prolong and aggravate the condition The pruritus recurs as the result of the same stimuli and the severity of the attacks varies with the severity of polycythemia vera present according to Brumpt The pruritus occurs more frequently in warm weather and the "fear of itching" may cause secondary symptoms such as thermophobia and claustrophobia He stated that the pruritus which is frequently intolerable may be relieved by cold the application of ether or eau de Cologne or by moderate physical exercise The vasomotor changes which dominate the pathogenesis [illegible]

[illegible] distended when vasodilatation is caused by heat and the pruritus ensues Torrey (687) described a 44 year old woman who had a "patch" of erythroderma on the anterior aspect of the right leg and a smaller one on the left leg From these areas many telangiectases extended into the more normal skin which had a mottled buff colored appearance She complained of pruritus and "burning sensations" in these regions

The patient described by Eichenlaub (161) presented a universal pruritic erythroderma Histologic examination showed mainly acanthosis edema of the papillae dilation of the lymph spaces and diffuse infiltration most marked in the papillary layer and around the blood vessels Following roent

onset a diagnosis of polycythemia vera had been made One of the cutaneous papules was injected with benzidine and elicited a "slight" positive reaction An acneiform papule was excised and immediately stained for oxydase The reaction was positive Hemograms disclosed 18 gm hemoglobin, 7,000,000 to 8,190,000 red blood cells and 10,350 white blood cells per cu mm The blood volume (Evans blue) showed plasma volume 2,994 cc and blood volume 7,879 cc (equals 115 7 cc per kg body weight) The hematocrit was 62 per cent, venous pressure 20 6 cm of water, and mean corpuscular volume 62 cu microns Biochemical examinations of the blood revealed 21 1 mg /100 cc urea nitrogen, 3 8 to 4 4 gm /100 cc albumin, and 3 49 to 3 98 gm /100 cc globulin The icteric index was 10 units and the bromosulfalein test showed 80 per cent retention Therapy consisted of venesection and deep roentgenotherapy to the spleen The radiation was administered in doses of 50 r each, three times a week, for a total of 10 treatments The following factors were employed 220 kv, 20 ma, time two and one-fourth minutes, F S D 50 cm total for 10 treatments 500 r

Eczema and dryness of the skin may be present in polycythemia vera and pruritus occurs frequently Dameshek (139f) stated that the possibility of polycythemia vera should be considered in persons who have intense pruritus following bathing He believed that pruritus was present in about one-third of the patients with polycythemia vera and this symptom *may be sufficiently severe so that 'ordinary"* bathing is contraindicated Although the cause of this symptom is not known, it appears to be specific for polycythemia vera and may be differentiated from the generalized constant pruritus associated with lymphosarcoma or Hodgkin s disease Brumpt (77) reported pruritus to be present in 22 of 30 patients having polycythemia vera Only purplish discoloration of the skin and splenomegaly were more frequent symptoms He believed that pruritus may sometimes be the initial symptom of polycythemia vera and may occur before the diagnosis is

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genotherapy and the administration of phenylhydrazine, the eruption disappeared but recurred in three months' time The red blood cell count remained stationary

Schamberg (601) reported a 57 year old man who had a generalized, scaly, eczematoid eruption and marked pigmentation of the skin Werther (722b) described a patient with pruriginous eczema

Sezary *et al* (626b) reported a 67 year old man who presented a diffuse red, dry, desquamating dermatitis, but no lesions of acne urticata The skin of the legs was sclerotic and atrophic Histologic examination of the skin from the leg showed thickening of the epidermis and a sclerotic cutis There were large vascular cavities filled with red blood cells which resembled hemangioma The cells of the vessels were thickened There were two types of infiltrate one was composed of histiocytes with occasional lymphocytes, the other of red blood cells A specimen from the chest showed enlargement and engorgement of the superficial capillaries, surrounded by an infiltration of histiocytes In the upper part of the cutis elastic fibers were absent, and there was a band of connective tissue similar to that seen in certain forms of sclerodermic atrophy

The patient described by Torrey (687) had a universal scaly, dark purplish red colored, pruritic erythroderma as well as edema of the hands feet and ankles which was primarily due to stasis and edema

II. Symptoms Related to Organic Changes in the Blood Vessels. The greater the hematocrit level, the slower the velocity of blood flow and, simultaneously the more viscous the blood, according to Dameshek (139c) Slow flow of blood may also result in disturbances of the extremities, particularly the feet The combined effects of sluggish blood flow, increased viscosity and the very high platelet level are undoubtedly responsible for the thrombotic manifestations which occur so frequently in polycythemia vera

Peripheral vascular lesions are the most common Dameshek (139c) found, but coronary thrombosis, cerebral thrombosis,

mesenteric thrombosis, hepatic vein thrombosis (Chiari syndrome), and even portal vein thrombosis may occur The peripheral vascular lesions may simulate thromboangiitis obliterans, according to Reznikoff *et al* (557b)

Arteriosclerosis appears to be more common in persons with polycythemia than in others of comparable age groups (139c) This may be due, in part, to the increased blood mass and the sluggish flow of blood The basal metabolic rate may be distinctly increased in these cases, but the hypermetabolism is not of the thyrogenous variety and is perhaps due to the great overproduction of blood cells, as in the hypermetabolism of chronic lymphocytic leukemia

Costello (127a) described a patient who had loss of directional power in the fingers of the left hand Hallam (254) reported a 57 year old woman who presented ulcerated nod

margin, and the blood viscosity was 2 5 times the normal The red blood cells numbered 6,420,000 per cu mm Rau *et al* (548) reported a 37 year old woman who had polycythemia, splenomegaly and ulcers of the legs

The erythema, edema and pain usually involve the distal portions of the feet or, less frequently, the hands or thorax, and are aggravated by palpation warm temperature, dependent position, or exercise, and are relieved by resting, cooling or elevation of the limb These symptoms may appear while the patient is at rest and disturb the sleep and they may be persistent or quite temporary The relief of pain by therapeutic measures which cause a reduction in the number of peripheral red blood cells, particularly if a considerable degree of anemia is produced, is often striking In one patient reported by Dameshek and Henstell (139b case 3), a diagnosis of erythromelalgia was considered for a period of "years" Since the sensation of warmth, pain and "tingling" of the legs is common in both polycythemia and erythromelalgia, the possibility

of polycythemia should be suspected when the diagnosis of erythromelalgia is considered

A patient reported by N. P. Anderson (9) was a 57 year old man who presented a classic picture of erythromelalgia associated with polycythemia vera He had noted that his feet became "tired" after walking and standing and finally they became so sensitive to heat and so painful that he was unable to walk more than a "few blocks" There was a violaceous redness of both plantar aspects in the region of the ball and heel

There was a painful violet colored discoloration of the last phalanges of two fingers in the patient reported by Grjasev (244) This discoloration faded after roentgenotherapy, which also caused a reduction in the number of red blood cells

The association of erythromelalgia and polycythemia was discussed by Parkes-Weber (502d) Scleroderma like lesions which resulted from organic changes in the blood vessels were noted by Ullman (692) and Sezary *et al* (626b)

The plethora and stasis of blood in all the peripheral vessels may account for the numerous paresthesias so typical of the disease, according to Harrop (260a) Thrombosis and phlebitis are very frequent and afford a possible explanation for the rather frequent association of erythromelalgia, as mentioned by Weintraud (717), Zadek (748a), Parkes Weber (502d), Preiss (538), Hollaender (291), Turk (690), Rosengart (576), and numerous others At times, gangrene of the foot or hand has been observed, and typical Raynaud's disease has been described, as reported bv Halir (252) The erythromelalgia is usually characterized by aggravation in the dependent position, when the skin color also deepens to a dark reddish cyanosis, often with edema, and with relief on elevation of the extremity Cold usually affords some relief and heat increases the pain Often the erythromelalgia is present when no abnormality is apparent on palpation of the blood vessels or on roentgenograms of the affected extremity Frequently, however, a considerable degree of arteriosclerosis is also present

Swartley *et al* (665) reported thrombosis and gangrene of the right arm, accompanied by massive swelling which extended to the wall of the chest, in a patient with polycythemia vera They cited seven other such cases from the literature in which thrombosis without gangrene occurred

III Symptoms Related to Heat and Cold. Brown and Giffin (76b) stated that the response of the capillaries of the skin to the increased volume of blood is twofold Distention and enlargement of part or all of the capillary loop, and the opening of all available capillaries In polycythemia vera, additional vascular space is utilized with a loss or impairment of the physiological heat mechanism of the skin One of the important functions of the skin is heat regulation Cold produces a closure of many of the vessels of the skin with a decrease in the radiation of heat When heat conversion is unnecessary, and when heat dissipation is advisable, a large number of resting capillaries are available In polycythemia this mechanism of heat regulation is impaired, since all available capillaries are continually functioning Many of the symptoms of polycythemia such as intolerance to heat and cold, a "burning" sensation of the skin, and the feeling of suffocation, are made clear by this conception of the impairment of the mechanism of heat regulation, they concluded

The delayed sluggish peripheral circulation no doubt accounts for the sensitivity to cold, of which these patients often complain, and probably for the lowered body temperature frequently described These patients nearly always feel better in a mild or warm climate, according to Harrop and Wintrobe (260b)

Pruritus is a frequent symptom, especially after bathing. These patients are intolerant to sudden changes in temperature and pruritus hiemalis occurs much more frequently in patients having polycythemia vera

Summary

The cutaneous lesions of polycythemia vera may be explained on a circulatory basis such as (56b) (1) Those re-

lated to vascular distention and increased viscosity of blood (purplish red color of the skin and mucous membranes hemorrhages, ecchymoses with resulting pigmentation, hemangioma, spider nevi, scrotal tongue, acne urticata, urticaria, pruritus, dry skin, eczema and erythroderma, (2) those related to organic changes in the blood vessels (thrombosis, ulcerated nodules of the legs, erythromelalgia, scleroderma like lesions), and (3) those related to heat and cold which become worse in a cold climate

IV. Relationship Between Polycythemia Vera and Leukemia. The relationship between polycythemia vera and leukemia has frequently been described It is known that the increased production of peripheral white blood cells in polycythemia vera may result in a malignant course, chiefly in the form of acute or chronic granulocytic leukemia Because leukemia is reported to occur in from 2 to 20 per cent of all cases of polycythemia vera, a discussion of this disease is included in this volume

However, some investigators, who do not agree with this opinion, believe that irradiation and the administration of P32, early in the course of polycythemia vera, may result in a leukemic process

Multiple myeloma associated with polycythemia vera was *reviewed by Lawrence and Rosenthal (373e) They found* three reports in the literature (Pribram 539 Perla and Biller 517, and Arnholdt 15) and described four additional cases

The polycythemic state frequently appears to become static for one year five years or longer, following a variable period of intense bone marrow activity when the peripheral blood count usually reaches a high level according to Dameshek (139e) Anemia which develops imperceptibly grad ually becomes more severe Fibrosis of the bone marrow gradually increases the white blood cells the megakaryocytes and the platelets, may remain at high levels or even increase in number, and early *leukocytes and nucleated red blood* cells are present Splenomegaly simultaneously becomes more

marked Dameshek believed the "agnogenic" myeloid metaplasia and the postpolycythemic state of myeloid metaplasia to be identical As the polycythemia progresses the white blood cells and finally the blood platelets decrease in number and hepatosplenomegaly increases causing discomfort sometimes marked pain and protuberance of the abdomen During this period treatment is merely symptomatic

Gans (210b) described a patient who had erythremia analogous to the cutaneous leukemic nodules These rose red colored firm irregular round or oval lesions involved the trunk particularly the lower part of the back and the abdomen They were markedly painful on palpation Histologic examination of a cutaneous lesion disclosed a mass of "peculiar" minute vascular dilatations packed with small round darkly stained nuclei which contained very little protoplasm These cells were oxydase positive Many of the small cutaneous vessels were completely thrombosed with marked overgrowth of the intima

Prognosis

Few diseases manifest the varied and bizarre course which occurs in polycythemia vera This disease is characterized mainly by its complications according to Tierney *et al* (654a b) and the prognosis is dependent upon the *type and* severity of these complications Early in the course of polycythemia the greatest danger appears to be from thromboses or emboli which may occur in the peripheral *cerebral coronary* pulmonary or intraabdominal vessels Because of their decreased resistance these patients are also prone to intercurrent infections

However *if these* complications have *not* occurred and the proper treatment is instituted the prognosis for polycythemia vera is good Among patients who *receive no treatment* the course is usually slowly progressive However spontaneous remissions sometimes of long duration may occur

It was the opinion of Dameshek (139c) that if the patient

lated to vascular distention and increased viscosity of blood (purplish red color of the skin and mucous membranes, hemorrhages, ecchymoses with resulting pigmentation, hemangioma, spider nevi, scrotal tongue, acne urticata, urticaria, pruritus, dry skin, *eczema and erythroderma*, (2) *those related* to organic changes in the blood vessels (thrombosis, ulcerated nodules of the legs, erythromelalgia, scleroderma like lesions), and (3) those related to heat and cold which become worse in a cold climate

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Treatment

It is generally agreed that the patient having polycythemia vera should be considered to be fundamentally "normal" Since these patients may have a long life span therapy should be as physiologic as possible, according to Dameshek (139c) Treatment may be directed toward diminution of the excessive overproduction of the bone marrow (roentgenotherapy, chemotherapy) or by removing the excessive blood from the circulation (phlebotomy)

Because patients with polycythemia vera frequently have vascular changes they are often "high strung nervous and irritable" according to Reznikoff (557a), and treatment should be directed toward the emotional complications as well as to the peripheral blood These patients are prone to the development of thrombosis and therefore moderate activity, rather than rest in bed is preferable Marked congestion of the mucous membranes also occurs and the possibility of irritation to these membranes should be avoided Reznikoff suggested that condiments concentrated alcoholic drinks "rough" food and hot food or drink should be avoided

The following principles for the management of polycythemia vera were listed by Wasserman (709)

1 Rapid reduction of blood volume to normal levels by phlebotomy (300 to 500 cc every two days)

2 Suppression of increased bone marrow activity with intravenous injections of P32 or TEM by mouth

3 Maintenance of cellular elements at normal levels which may be ascertained by complete hemograms every four to six weeks

4 Overtreatment should be avoided No more than 5 to 7 mc of P32 should be administered by intravenous injection during a six month period The first course of TEM should start with 10 mg and should not be repeated for two months Phlebotomy should be performed on patients who are resistant to other forms of therapy

5 Unless the disease has been controlled, elective surgery is contraindicated

with polycythemia lives long enough the bone marrow will gradually show signs of diminished activity regardless of the cause of the constant and excessive hematopoiesis When this occurs the red blood cells decrease in number and a certain degree of fibrosis develops With the increasing reduction of erythropoietic tissue myelofibrosis becomes more marked and in extreme cases the marrow becomes an organized mass of fibrous tissue which may be due in part to an actual proliferation of fibrous tissue

The leukocytic production at first unaffected may also become diminished while the megakaryocytes usually remain and are markedly "conspicuous in the lack of other cell types" Nucleated red blood cells increased polychromatophilia and various types of immature granulocytes are present in the peripheral blood The continued myelopoiesis either results in or is associated with extramedullary hematopoiesis in the spleen and to a lesser extent in other organs Marked splenomegaly occurs and is composed largely of metaplastic marrow tissue (myeloid metaplasia) The excessive immaturity of the red and white blood cells may be due to the lack of normal regulatory effect of the spleen when involved by myeloid metaplasia according to Dameshek The continuing myelofibrosis leads to increasing anemia and finally to increasing leukopenia granulocytopenia and thrombocytopenia Although the anemia is temporarily ameliorated by transfusions of whole blood it later becomes uncontrollable particularly when hemorrhages resulting from a deficiency of blood platelets supervenes and death follows Spontaneous bleeding does not usually occur in polycythemia vera except after trauma such as from injury or operative procedures Large hematomas may occur following surgery and excessive bleeding may follow dental extractions tonsillectomy polypectomy or similar procedures The cause of this hemorrhagic tendency remains obscure and despite the known fact that the blood platelets are at a high level there is no apparent abnormality of the blood capillaries or proof of any well demonstrated abnormality of the coagulation factors of the blood (139c)

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5 Unless the disease has been controlled, elective surgery is contraindicated

with polycythemia lives long enough the bone marrow will gradually show signs of diminished activity, regardless of the cause of the constant and excessive hematopoiesis When this occurs, the red blood cells decrease in number and a certain degree of fibrosis develops With the increasing reduction of erythroproietic tissue, myelofibrosis becomes more marked and, in extreme cases, the "marrow becomes an organized mass of fibrous tissue,' which may be due, in part, to an actual proliferation of fibrous tissue

The leukocytic production at first unaffected, may also become diminished, while the megakaryocytes usually remain and are markedly "conspicuous in the lack of other cell types' Nucleated red blood cells, increased polychromatophilia and various types of immature granulocytes are present in the peripheral blood The continued myelopoiesis either results in, or is associated with, extramedullary hematopoiesis in the spleen and, to a lesser extent, in other organs Marked splenomegaly occurs and is composed largely of metaplastic marrow tissue (myeloid metaplasia) The excessive immaturity of the red and white blood cells may be due to the lack of normal regulatory effect of the spleen when involved by myeloid metaplasia, according to Dameshek The continuing myelofibrosis leads to increasing anemia and finally to increasing leukopenia, granulocytopenia and thrombocytopenia Although the anemia is temporarily ameliorated by transfusions of whole blood it later becomes uncontrollable particularly when hemorrhages resulting from a deficiency of blood platelets supervenes, and death follows Spontaneous bleeding does not usually occur in polycythemia vera except after trauma such as from injury or operative procedures Large hematomas may occur following surgery and excessive bleeding may follow dental extractions, tonsillectomy, polypectomy, or similar procedures The cause of this hemorrhagic tendency remains obscure and despite the known fact that the blood platelets are at a high level, there is no apparent abnormality of the capillaries or proof of any well demonstrated abnormality of the coagulation factors of the blood (139c)

1 When the peripheral red blood cells exceed 7,500 000 per cu mm venesection is performed 1 000 cc of blood are removed every 48 hours until the erythrocytes have decreased to 6 000 000 cells per cu mm

2 P32 is administered in the following initial dosage (for parenteral administration these dosages are decreased 25 per cent)

Initial Number of Red Blood Cells Per Cu Mm	*Strength According to the United States Bureau of Standards*
More than 9 000 000	4 5 mc
More than 8 000 000	4 0 mc
More than 7 000 000	3 5 mc
Less than 7 000 000	3 0 mc

When the blood platelet level is not elevated the dosage is decreased one mc

3 Parenteral administration Food is not to be ingested for six hours prior to therapy and for three hours following therapy The patient should be encouraged to drink water but no "soft" drinks should be given Iron and phosphate medications are discontinued for 24 hours prior to and following P32 therapy P32 is not administered orally to patients having frequent bowel movements

4 A hemogram which includes red blood cell white blood cell and platelet counts should be done monthly

5 Additional P32 therapy should not be administered more often than every two months

6 The amount and frequency of subsequent therapy should be determined by the response to the first treatment

7 P32 should not be administered when the blood platelet count is less than 150 000 per cu mm (indirect method) when the reticulocytes are less than 0 2 per cent or when the peripheral white blood cells are less than 3 000 per cu mm

8 Adequate protective measures should be utilized by all personnel

According to Lawrence *et al* (373b), it is difficult to evaluate the comparative end results of any of these therapeutic measures because no large group of patients treated by one method have been studied for a sufficient period to determine the length of the resulting remission and the average survival rate after onset of the disease or institution of therapy

It was aptly stated by Dameshek (139c) that all present therapeutic methods for polycythemia vera are "relatively crude" He concluded that "A more rational approach would be to limit the unknown factors which bring about the excessive blood production Until these factors are found the therapeutic method used should be both as physiologic as possible and free of immediate and possible future harm"

I. Irradiation Therapy.

1 ROENTGENOTHERAPY Roentgenotherapy has been employed for polycythemia vera for many years but this form of therapy was not regarded favorably until recently (139c) Subsequently, "spray" irradiation, or roentgenotherapy to the entire body, were regarded to be "effective and well tolerated" High voltage roentgenotherapy, given over the bones or in "spray" form, has been used for approximately the past 30 years and prolonged remissions have been reported following 'spray" irradiation Irradiation of the bone marrow, spleen, or both, is administered in doses of approximately 50 r at each treatment The location of this "spot" irradiation varies one exposure may be directed over the sternum, one over the long bones, over the spleen, or to other areas of the body.

2 RADIOACTIVE PHOSPHORUS Radioactive phosphorus (P32) was introduced by Erf and Lawrence (168c) as a means of administering ionizing ray (beta ray) activity to the bone marrow cells The reports indicate that remissions of from three months to three years have been obtained following therapy with radioactive phosphorus

A standardized form of P32 therapy for polycythemia vera was suggested by Wiseman *et al* (739c)

1 When the peripheral red blood cells exceed 7 500 000 per cu mm venesection is performed 1 000 cc of blood are removed every 48 hours until the erythrocytes have decreased to 6 000 000 cells per cu mm

2 P32 is administered in the following initial dosage (for parenteral administration these dosages are decreased 25 per cent)

Initial Number of Red Blood Cells Per Cu Mm	*Strength According to the United States Bureau of Standards*
More than 9 000 000	4 5 mc
More than 8 000 000	4 0 mc
More than 7 000 000	3 5 mc
Less than 7 000 000	3 0 mc

When the blood platelet level is not elevated the dosage is decreased one mc

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4 A hemogram which includes red blood cell white blood cell and platelet counts should be done monthly

5 [illegible]

[illegible] bsequent therapy should be determined by the response to the first treatment

7 P32 should not be administered when the blood platelet count is less than 150 000 per cu mm (indirect method) when the reticulocytes are less than 0 2 per cent or when the peripheral white blood cells are less than 3 000 per cu mm

8 Adequate protective measures should be utilized by all personnel

Wright (743) believed the radioactive isotope of phosphorus (P32) to be the treatment of choice for polycythemia vera Because the maximum decrease in the number of peripheral red blood cells does not occur until 40 to 60 days following administration of P32, venesection is frequently employed *for initial control of a new case to afford immediate* symptomatic relief He stated that, although therapy should be individualized to each patient, 3 mc of P32 in the form of sodium dihydrogen phosphate may be given orally in the "average case" The hematologic picture should then be studied during the following two to three weeks before additional therapy is administered The most frequent complications of polycythemia vera are intravascular thrombosis and hemorrhage The entire blood circulation is "slow or sluggish' and the impeded hepatic circulation is manifested by low fibrinogen and prothrombin levels Occasionally this hypothrombinemia causes severe hemorrhage when there is involvement of an intracranial blood vessel If the vitamin K level is not reduced the prothrombin returns to normal levels after correction of the increased viscosity, according to Wright

Best and Limarzi (45b) found that approximately 50 per cent of the patients with polycythemia vera die from hemorrhage or thrombosis The median life expectancy after onset of symptoms was approximately seven to eight years and these patients rarely lived for 15 to 25 years They believed radioactive phosphorus to be the most simple and effective method for irradiation of the bone marrow They found that most investigators employed an initial dose of 3 to 8 mc P32, with or without venesection, which usually offered adequate remissions, although many patients required repeated doses with a total up to 20 mc Older patients were often found to respond favorably to smaller amounts of P32 than younger patients Remissions from this therapy last from months to years' but in most cases a second course is required in from six to 10 months Subsequent remissions which usually become increasingly longer, may ultimately average about three years The remissions usually produce marked symptomatic

improvement including decrease of the splenomegaly Best and Limarzi stated that while the administration of larger initial doses ("as much as 12 mc for the first treatment") tends to hasten and prolong the remission it also increases the danger of bone marrow aplasia and is "best avoided by the casual therapist" They found that the mortality from hemorrhage and thrombosis has been decreased by 50 per cent with the advent of P32 therapy and the majority of patients having polycythemia vera live for five to 20 years after the onset of symptoms with a median survival of 13 2 years when treated with P32 (Lawrence *et al* 373b) Whether the administration of P32 has increased the mortality rate for acute granulocytic leukemia "is still open to question" according to Best and Limarzi However they believed that if this were the case the increase was relatively slight and this factor would be "far outweighed by the reduction in other serious complications increased general sense of well being and general prolongation of survival consequent to the use of this agent

Radioactive phosphorus is probably the most effective therapy for polycythemia vera and produces long remissions without causing nausea vomiting or other untoward affects when administered in therapeutic doses according to Limarzi (391b) He stated that radioactive phosphorus emits a beta ray has a half life of 14 3 days and is localized in a large measure in the bone marrow and blood forming tissue It is usually administered as a sodium acid phosphate preferably by intravenous injection to eliminate the "uncertainty of gastrointestinal absorption" The initial dose is from 3 5 to 7 mc but if hematologic and symptomatic remissions have not occurred from three to six months later another dose comparable to or a fraction of the initial dose is then administered In patients having severe symptoms or a possibility of thrombosis 500 cc of peripheral blood is removed every second day until the hematocrit has been reduced to about 40 per cent Limarzi believed that complete hematologic and symptomatic remissions lasting from six months to five years

could be produced with radioactive phosphorus therapy The untoward effects of this treatment are usually severe leukopenia thrombocytopenia and anemia which result from over doses or occur in patients who are unusually sensitive to this drug Although about 10 per cent of the patients with polycythemia vera develop chronic leukemia particularly the granulocytic type even though irradiation or radioactive phosphorus were not administered several cases have been reported in which polycythemia vera terminated in acute leukemia following radioactive phosphorus therapy

S O Schwartz and Ehrlich (615d) reviewed the literature with regard to the coincidence of polycythemia vera and leukemia They found reports of 30 patients who had polycythemia as well as leukemia Among these 25 had received irradiation therapy for polycythemia vera prior to the development of leukemia They believed that leukemia occurred in these patients as a result of the previous irradiation therapy for the polycythemia vera All of these patients in whom leukemia occurred following radioactive phosphorus therapy had acute granulocytic leukemia

Reinhard (552) reported that among 130 patients with polycythemia vera treated with P32 two had a terminal leukemia These two patients had required considerably larger doses of P32 at much more frequent intervals for control of the polycythemia vera than other patients with this disease who were given the same type of therapy He believed the most satisfactory therapy would be to administer radioactive phosphorus to all patients with severe polycythemia vera at the first examination since prolonged remissions lasting three four five or even six years is obtained by a single course of treatment in some cases However in the event of an early flare up or if unusually large amounts of radioactive prosphorus appear to be required for control of the disease Reinhard believed that some other less dangerous form of therapy should be used He stated that radioactive phosphorus should be employed routinely until it has been determined whether an occasional course of treatment

over a period of many years will control polycythemia vera However, if this is not found possible, and increasingly high doses are necessarily being administered, other forms of therapy, such as phlebotomy, are advocated

Although the administration of radioactive phosphorus for the treatment of polycythemia vera has been widely advocated, other investigators including Craver (130c) and Dameshek (139c) have stressed the need for caution in the use of this drug

Craver stated that "although P32 is currently considered by many as the treatment of choice for polycythemia vera I think we should never lose sight of the fact that in giving it we are putting into a patient a radioactive material, active all over the body and continuing to be active, with its exponential rate of decay, for a long time despite the relatively brief half life of two weeks We should think twice before committing this iatric insult, especially to an individual who may have a relatively stable type of polycythemia, with perhaps a prognosis of several to many years of life This consideration appears however, to be a theoretical one A few years ago there was expressed in some circles a fear of inducing the conversion of leukemia in cases of polycythemia vera treated by P32 Statements have been made in the literature to the effect that no case of polycythemia undergoes a conversion to leukemia unless subjected to some type of radiation While it is probably true that in the past two or three decades most cases of polycythemia have been treated at some time in their course with some type of radiation, I am nevertheless inclined to agree with those who look upon polycythemia as the erythropoietic analogue of leukemia, and to believe that a certain proportion of them will undergo change to leukemia, no matter what the method of treatment Furthermore, aside from the withdrawal of blood, P32 does seem to be our best present resource of treatment of polycythemia vera"

The use of roentgen rays and radioactive phosphorus for the treatment of polycythemia vera "should be approached with a certain degree of caution" according to *Dameshek*

(139c) Although roentgen rays and radioactive substances are known to have leukemogenic and carcinogenic properties when the "rather vaguely defined safe dosage" is exceeded, it is not yet known whether the ordinary dosages employed for the treatment of polycythemia vera are harmful or productive of leukemia Among the few cases of leukemia which occurred with polycythemia vera and were treated by some means other than roentgenotherapy or received no treatment, the reports are "confused by the frequent listing as leukemia of the leukemoid state of myelofibrosis with myeloid metaplasia" Dameshek stated that among 50 "reasonably well followed cases of polycythemia," acute leukemia occurred in only one patient who had no previous roentgen ray or radioactive phosphorus therapy In another series of 100 patients who had not received roentgen ray or radioactive phosphorus therapy, acute leukemia was known to have occurred in one patient, according to Dameshek However, at this same clinic, four patients who had been treated with radioactive phosphorus died from acute leukemia Lawrence and Reinhard (552) reported a similar incidence of acute leukemia following radioactive phosphorus therapy which they believed to be "within normal limits for the development of leukemia in patients having polycythemia Dameshek believed that 'time alone and the comparison of large numbers of well documented cases in which patients are treated with and without radioactivity should determine whether or not this therapeutic method is leukemogenic He restricted the use of intravenous radioactive phosphorus to patients having frequent thrombosis together with a marked elevation of blood platelets and to those who were unusually resistant to venesection He found there was a satisfactory reduction of blood platelets in patients who had thrombocytosis following radioactive phosphorus therapy and this treatment usually resulted in a prolonged remission with amelioration in the thrombotic tendency

Klemperer (344) described a patient who had been treated for polycythemia for 11 years During the last year he had

received radioactive phosphorus therapy after which the peripheral blood count revealed 10 000 white blood cells per cu mm with 64 per cent "blast" cells

II Chemotherapy

1 NITROGEN MUSTARD Nitrogen mustard (methyl bis [beta chloroethyl] amine hydrochloride) has been used for the treatment of polycythemia vera Doses of 0 1 mg per kilogram of body weight, in 10 cc isotonic sodium chloride solution are either administered daily by intravenous injections for four consecutive days or 0 2 mg per kilogram of body weight is given on two consecutive days Limarzi (391b) reported symptomatic and hematologic remissions which lasted from six months to two and one half years following nitrogen mustard therapy Symptomatic relief may occur within three weeks after treatment and hematologic values may be within normal limits two months after treatment in some cases The *administration of nitrogen mustard is not difficult and requires* no "elaborate set up" according to Limarzi but may cause toxic reactions such as nausea vomiting leukopenia or thrombocytopenia

2 TRIETHYLENE MELAMINE (TEM) Triethylene melamine like radioactive phosphorus and nitrogen mustard causes a reduction in the total red blood cells inhibits the bone marrow and reduces the number of thrombocytes Thrombocytopenia contributes to the hypercoagulability and abnormal clot formation and retraction which according to N Rosenthal and R L Rosenthal (578b) when aggravated by the presence of an elevated hematocrit percentage may lead to either hemorrhage or intravascular thrombosis They studied 30 patients with polycythemia vera for an average of more than one year following triethylene melamine therapy These patients were given TEM by mouth one hour before breakfast in doses of 2 5 to 5 0 mg every one to three days until they had received a total dosage of 15 to 40 mg Additional doses were given two to three months later depending upon the hematologic response No untoward reactions from this drug

were noted, except for occasional nausea They noted that the symptoms usually disappeared as the red blood cell count and the hematocrit percentage decreased and the lowest erythrocyte, hemoglobin and hematocrit levels were usually reached four months after therapy The conclusions of this study were that TEM has good potentialities in the treatment of polycythemia vera, although longer follow up studies are required before its value can be compared with that of radioactive phosphorus They found that older patients whose disease was of long duration and who had elevated peripheral blood cell and thrombocyte counts, appeared to show less favorable response to triethylene melamine therapy than patients in whom the disease was of short duration and who had minimal previous therapy and normal numbers of peripheral blood cells and thrombocytes

Best and Limarzi (45b) stated that about two thirds of all the patients who receive TEM therapy for polycythemia vera show a decreased red cell mass and improvement of their symptoms They used doses of 5 mg twice a week until the hematocrit reading was reduced to below 45 per cent Treatment was then discontinued until the hematocrit level again became elevated When the hematocrit showed only slight elevation, smaller doses of 2 to 4 mg a week were given and occasionally a maintenance dose of 1 to 2 mg a week was required to maintain a remission However, remissions of more than one year occurred without maintenance doses They had successfully treated more than 30 patients with triethylene melamine which was often combined with venesection However, they stressed the possibility of the occurrence of severe bone marrow aplasia Should this occur, the hematocrit, white blood cell count and platelet levels should be determined frequently during active therapy They concluded that P32 appeared to be the most satisfactory agent for the treatment of polycythemia vera but TEM may be used in the management of this disease when P32 is not available

3 DARAPRIM® Daraprim is an antimalarial drug with

antifolic acid properties Symptomatic and hematologic improvement of polycythemia vera have been produced by the administration of Daraprim (2-4 diamino 5 p chlorophenyl-6-ethylprimidine) This folic acid antagonist is reported to produce anemia and arrest of megaloblasts in the bone marrow of normal persons Daraprim, in doses of 2.5 mg a day by mouth, was administered to six patients with polycythemia by Frost and Jones (203) They reported remission of symptoms decrease in the hematocrit and hemoglobin levels, as well as in the total number of red blood cells, white blood cells and platelets

However, Best and Limarzi (45b) were of the opinion that an appraisal of the therapeutic value of this drug cannot be made at this time

III. Phlebotomy. Phlebotomy, or venesection, has been found to be a satisfactory form of treatment for polycythemia vera The red blood cell mass, which is the hematocrit reading multiplied by the blood volume, should be determined before phlebotomy, since it is usually greatly increased in polycythemia vera This therapy is regarded to be "safe" when the hematocrit indicates 45 cc of red blood cells per 100 cc of blood, according to Dameshek (139c) He found that "well planned, multiple venesections" result in reduction of the red cell mass to normal but iron deficiency causes the erythrocytes to be poorly hemoglobinized Although the mature red blood cells may continue to increase in number, they are of small size hypochromic and, therefore, greatly reduced in volume 500 cc of blood may be removed twice weekly by phlebotomy and four to eight venesections may be required to reduce the hematocrit to a normal level of about 45 per cent Following venesection when the hematocrit is approximately 45 to 48 per cent and the hem ... 85 per cent (13 3 gm), ... (red meats, liver, eggs, ... ach, string beans, swiss chard, and brown cereals such as hominy, oatmeal, whole wheat, bran, and shell fish including oysters, clams and lobsters) should be markedly curtailed Instead, the patient is

instructed to eat fish, fowl, lamb and veal and to drink two to four glasses of milk a day to maintain the necessary protein requirements Within three to 18 months or more after phlebotomy, the hematocrit levels again increase to over 50 per cent and the symptoms of headache, vertigo and fatigue usually recur, according to Dameshek (139c) Two to three venesections may then be required to reduce the hemoglobin and hematocrit levels to normal He believed this regimen could control the symptoms of polycythemia vera 'for a few to many years' since he had observed patients for from 10 to 15 years whose health was comparable to "that of normal persons in the same age group"

IV. Drugs not in General Use.

1 PHENYLHYDRAZINE This drug was formerly considered to be the treatment of choice for polycythemia vera but is no longer considered to be a useful therapeutic agent Phenylhydrazine acts to remove the excessive amounts of blood from the circulation by the induction of excessive hemolysis However, it has been found difficult to control the effects of the drug and the products of hemolysis are retained within the body causing excessive strain on all the avenues of both blood production and destruction' according to Dameshek (139c) Because of its prolonged action after administration has been discontinued and because of possible injury to the liver cells, phenylhydrazine should be administered with great caution

Treatment with acetylphenylhydrazine was discussed by Zeiter (751) He stated that 0 1 gm is given in capsule form once a day for seven days The red blood cell count is determined each week and as the cells decrease the dosage is decreased until the proper one, which will maintain a reduced cell concentration and alleviate symptoms is found He believed this drug to be effective in causing hemolysis of the red blood cells and the dose should depend upon the red cell mass to be destroyed *Usually 0 1 gm is given three times a day* for from 10 to 30 days and since this drug action persists for seven to 10 days after it is discontinued, it is important to fol-

low the red cell mass closely to prevent marked anemia It is suggested that the drug be discontinued when the red blood cells have been reduced to 5 500,000 per cu mm During treatment with this drug, mild jaundice may occur and the urine becomes dark in color, due to destruction of the red blood cells

2 ARSENIC According to Limarzi (391b), arsenic in the form of potassium arsenite solution (Fowler's solution) is a safe and reliable treatment for polycythemia Arsenic will depress the red blood cell formation and has been reported to be effective when given in doses of 0 2 cc, three times a day, with or after meals, in water or fruit juice The dosage is then increased 0 06 cc each day (not each dose), until 0 6 cc are being taken three times a day If anorexia occurs, the arsenic is discontinued for two days, when doses of two thirds to three fourths of the dose which produced anorexia are given, and this dose is maintained

The disadvantages of therapy with Fowler's solution appear to be the untoward reactions to the drug These usually include loss of appetite nausea and vomiting followed by loss of weight and gastrointestinal discomfort

THE DIAGNOSIS OF LEUKEMIA

By

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I. Introduction

The diagnosis of any disease is dependent upon the presence of certain clinical characteristics and the demonstration of either a specific etiologic factor, or typical histologic changes Although the exact etiologic agent of leukemia is still not known, the anatomic and cytologic changes which occur in the typical forms of this disease are not difficult to identify Involvement of the peripheral and abdominal lymph nodes, liver and spleen are often apparent on palpation In most cases of leukemia the abnormal cells, which are present in the bone marrow and other organs of the reticuloendothelial sys

We are indebted to Mr Thomas Scanlan of the Chicago Medical School for preparing the illustrations and to Miss Helen Legere Gant for her technical assistance

tem, enter the blood stream in excessive numbers and result in an increase of white blood cells The additional findings of anemia and thrombocytopenia may reflect the leukemic process and replacement present in the bone marrow If the proper technic for obtaining and staining the blood films is used, and a competent interpretation is made, these cells may be identified and thus confirm the diagnosis of leukemia Therefore, we have included detailed descriptions of the laboratory technics essential to obtaining proper blood films and bone marrow material

[illegible] type of leukemia

TABLE I

Classification of Leukemia

A Acute and Subacute Leukemia

1. Acute Lymphocytic Leukemia
2. Acute and Subacute Granulocytic Leukemia
3. Acute Monocytic Leukemia
4. Stem Cell Leukemia
5. Plasmacytic Leukemia
6. Erythroleukemia

B Chronic Leukemia

1. Chronic Granulocytic Leukemia
2. Chronic Lymphocytic Leukemia
3. The "Leukemic" Phase of Lymphosarcoma
4. Chronic Monocytic Leukemia (Reticuloendotheliosis)

II. Acute Leukemia

1. Introduction

There are certain typical clinical features which occur in all forms of acute leukemia The identification of the type of acute leukemia present may be established by the characteristic cytology and certain clinical features peculiar to that type The differentiating features of each type will be discussed following this general review of the entire group

The cytologic picture of acute leukemia reveals immaturity of the cells and the predominant cell is the primitive leukocyte, or blast cell These blast cells may sometimes be identified by certain cytologic criteria, such as the number of nucleoli, the presence or absence of Auer bodies the staining

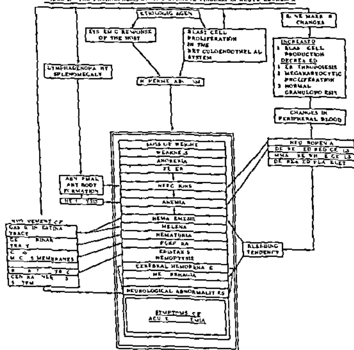


Figure 153 Auer bodies

properties of the cytoplasm, and the character of the nuclear chromatin However, they can frequently be identified by the type of the more mature cell which is usually present When the blast cell has no identifiable characteristics, and there are no mature cells, the condition is designated "stem cell leukemia"

The onset of the clinical symptoms of acute leukemia are usually acute and "explosive" All of the symptoms listed in Table II may occur However, the onset may be insidious, even though there is a leukocytosis with a predominance of blast cells Physical examination may reveal no involvement, or minimal involvement, of the reticuloendothelial system Anorexia, a slight loss of weight, mild anemia, arthralgia, fever

TABLE II THE PATHOGENESIS OF THE CLINICAL FINDINGS IN ACUTE LEUKEMIA



and night sweats may remain the only presenting symptoms for a period of weeks, or even months

The presenting symptom may be a severe septicemia, coincident to a diminution in the number of neutrophils or abnormal reticuloendothelial function Pyogenic foci, such as furuncles, pulmonary infections, acute endocarditis, or even meningitis, may eventually develop

A generalized bleeding tendency (due to thrombocytopenia) with purpura and hemorrhagic episodes may be the initial symptom in some patients Hemorrhage from the gastrointestinal tract alone occurs occasionally and, unless the proper diagnosis is made, surgical intervention may result in generalized bleeding In acute leukemia, the bleeding may not be due only to the thrombocytopenia Various defects in the coagulation mechanism, such as fibrinolysin activity, thrombasthenia or, rarely, circulating anticoagulants, have been demonstrated

In some cases the clinical manifestations have been even more diverse and misleading There are reports of neurologic manifestations, uremia, or intrahepatic involvement with jaundice, as the presenting symptom of acute leukemia

There are two entities which are closely allied to acute leukemia They are "aleukemic" or "subleukemic" leukemia and the "preleukemic" state "Aleukemic" is used to designate the form of leukemia in which there are no leukemic cells in the peripheral blood and the total number of white blood cells is either normal or reduced Since careful study of the blood film will usually disclose small numbers of these cells we favor the designation 'leukopenic phase of leukemia' The diagnosis in these cases may be further complicated by the minimal physical signs present

However, the following signs and symptoms may frequently lead to the suspicion of a leukemic process (Table II)

1 Hypermetabolism manifested by fever, night sweats, loss of weight, and generalized weakness

2 A decrease in the production of red blood cells platelets, and normal granulocytes, with resulting anemia, thrombocytopenia, and neutropenia

3 Involvement of the reticuloendothelial system (lymphadenopathy, hepatomegaly, splenomegaly)

Although these symptoms and signs may also be present in a number of diseases, an awareness of the leukopenic phase of leukemia will eliminate needless laboratory studies for other conditions When a leukemic process is suspected, the diagnosis can usually be confirmed by examination of the sternal bone marrow, except in the "preleukemic" stage of the disease

This "preleukemic" state presents even greater difficulty in diagnosis than the leukopenic phase The recognition of this form resulted from retrospective studies of many cases in which the diagnosis of leukemia could not be made either clinically or cytologically However, these patients eventually had a typical leukemia The presenting symptoms are usually fever, loss of weight, malaise, and an unexplained anemia Leukopenia is very frequent and, as a result, furunculosis, cystitis, pyelonephritis and acute respiratory infections occur A preleukemia or early leukemic state should always be suspected when both leukopenia and pyogenic infection are present Usually a definite diagnosis cannot be made from study of the bone marrow There may be a significant increase of reticulum cells, as well as a shift to the left of granulopoiesis with a predominance of less mature cells but no significant increase of blast cells However, these changes occur in a number of other diseases, including viral and chronic pyogenic infections granulomas or even neoplasms There may also be hypoplasia of the bone marrow, such as that which occurs in "overwhelming" infections drug intoxication or drug sensitivity In some cases a hypersplenic state is simulated, so that peripheral thrombocytopenia, with adequate or increased numbers of megakaryocytes are present in the bone marrow, or there may be a hemolytic process with accelerated erythropoiesis of the marrow Occasionally megaloblastic changes in the erythroblasts will result in unsuccessful treatment for "pernicious anemia"

It is essential to be aware of these confusing changes and

findings and it is necessary to make repeated attempts, at reasonable intervals of time, to establish a diagnosis The study of these findings will also aid in a better understanding of the natural history and course involved in the metamor phosis of leukemic states

The significance of this so called preleukemic state is perhaps of even greater importance The designation given to this condition is a misleading one In some cases careful histologic studies may reveal areas of leukemic involvement, while in others no leukemic infiltrate is present However, the occurrence of various signs (leukopenia, hemolysis, and others) are indicative of a disease process It is quite possible that the etiologic agent of leukemia is capable of involving all tissues of the body, including the reticuloendothelial system, prior to the appearance of specific cytologic characteristics Therefore, we believe that leukemia is a systemic disease which does not always present an identifiable pathology

2. *Specific Types of Leukemia (Table III)*

A Acute Lymphocytic Leukemia This type of leukemia usually occurs in the first, but occasionally in the second, decade of life This is the most frequent type to affect children The onset is usually insidious and has a more prolonged

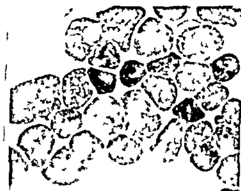


Figure 154 Acute lymphocytic leukemia (bone marrow) Note the dense chromatin in the nuclei and the neighboring mature lymphocytes and smudge cells (degenerated forms of lymphocytic cells) (Oil immersion)

course than other acute leukemias (six months to three years) The initial symptoms are usually fever malaise and arthralgia Prominent lymphadenopathy and splenomegaly are usually present and a bleeding tendency with petechiae and ecchymoses is frequent The predominant cell in the peripheral blood and bone marrow is the lymphoblast In some cases the bone marrow may show a rather nonspecific picture with only a suggestive increase in primitive cells In other cases, this picture may remain aplastic for some time preceding the typical infiltration of lymphoblasts Clinically infectious mononucleosis infectious lymphocytosis lymphocytosis of pertussis and chronic infections should be considered in the differential diagnosis

B Acute Granulocytic Leukemia Although this type of acute leukemia may occur at any age there is a slight predominance from the third to fifth decades The onset is fre-

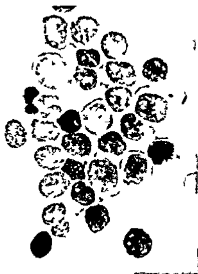


Figure 155 Acute granulocytic leukemia (bone marrow) Finer chromatin structure with lighter cytoplasm containing amoeboid protrusions (O I immersion)

TABLE III

Type of Leukemia	*Cytology*	*Age Group*	*Onset*	*Clinical Course*
Acute Lymphocytic	Lymphoblast Coarse granular chromatin one or two nucleoli basophilic cytoplasm no granules in cytoplasm	First decade Occasionally second decade	Insidious	Spontaneous remissions and exacerbations
Acute Granulocytic	Myeloblast Fine nuclear chromatin 3 to 5 nucleoli few granules Auer bodies in cytoplasm	All ages	Acute	Progressive
Subacute Granulocytic	Increase of myelo blasts promyelocytes and myelocytes with few mature cells	Fourth and fifth decades	Subacute	Progressive
Erythro leukemia	Immature erythroblasts and granulocytes	All ages	Acute or insidious	Progresses to acute or subacute granulocytic or monocytic leukemia
Acute Monocytic	Monoblast Irregularly shaped folded nucleus Lacy reticular chromatin inconspicuous nucleoli azure granules	Fourth to sixth decades	Rampant	Fulminating
Lymphoma (Leukemic Phase)	Abnormal lympho blast Kidney shaped or notched nucleus Coarse reticular nucleus	Third decade or later	Acute toxic	Progressive
Stem Cell	No distinguishing features	All ages		Like acute granulocytic or other acute leukemias
Plasmacytic	Plasmablasts			Dependent upon course of underlying multiple myeloma

Duration	Distinguishing Clinical Features	Atypical Characteristics	Differential Diagnosis
6 months to 3 years	Arthralgia Fever and malaise Moderate lymphadenopathy and splenomegaly Petechiae and ecchymoses	Leukopenia Lack of primitive forms in peripheral blood	Infectious mononucleosis Infectious lymphocytosis Severe protracted viral infection Lymphosarcoma (leukemic phase)
3 to 6 months	Severe weakness Active hemorrhagic phenomenon Infiltration of skin and gums Sepsis frequent Minimum lymphadenopathy and splenomegaly	Resembles chronic sepsis with pancytopenia Reticulum cell infiltration in bone marrow Simulates hemolytic or megaloblastic anemia	Hypersplenism Atypical hemolytic or megaloblastoid processes So-called "refractory" anemia Pancytopenia without typical bone marrow
6 to 12 months	Similar to acute granulocytic leukemia, except for marked splenomegaly	As in acute granulocytic leukemia	
3 to 9 months	Similar to acute and subacute granulocytic leukemia		
Weeks to several months	Severe toxemia and sepsis Extensive involvement of skin and gums Minimal lymphadenopathy and splenomegaly Active bleeding episodes	Leukopenia Chronic sepsis Bizarre cutaneous manifestations Reticulum histiocytic and monocytoid infiltration of bone marrow	Chronic infection. Granulomas Unusual dermatoses
3 to 6 months	Asymmetrical peripheral and visceral lymphadenopathy Severe systemic manifestations	More gradual onset May simulate severe acute viral infection Hemolytic anemia	Acute leukemias especially lymphocytic Infectious mononucleosis Plasmablast leukemia



Figure 156 Cells in mitotic division Acute granulocytic leukemia

quently acute and the course is progressive and short (three to six months) The initial symptoms are usually marked weakness, malaise, and frequent attacks of sepsis There are often changes in the gums which appear spongy and hypertrophied, as well as cutaneous infiltrations Active hemorrhagic phenomena, such as epistaxis and bleeding from the gastrointestinal tract, occur frequently Minimal splenomegaly and lymphadenopathy are the rule in this type of acute leukemia Marked splenomegaly usually indicates that chronic granulocytic leukemia is developing into the acute phase The pathognomonic cell in the peripheral blood and bone marrow is the myeloblast This cell can often be differentiated from other blast cells by the presence of reddish rods in the cytoplasm which are called Auer bodies (See Fig 153)

The atypical presenting symptoms may be chronic sepsis accompanied by neutropenia, anemia, and thrombopenia The bone marrow may sometimes reveal an atypical picture consisting of a peculiar infiltration of reticulum cells Occasionally the blast cells are not recognized as myeloblasts and are thought to be early erythroblasts Erythropoiesis may be

markedly accelerated and have a megaloblastic like appearance Therefore, such conditions as hypersplenism, "refractory or aregenerative anemia," or other causes of hemolysis and megaloblastic anemia, are considered in the differential diagnosis

C SUBACUTE GRANULOCYTIC LEUKEMIA The clinical features of this entity are quite similar to those of acute granulocytic leukemia However, this type occurs most frequently in the fourth and fifth decades of life and, although the course is progressive, it is less acute (six months to one year) Splenomegaly is more pronounced than in the acute form Although the myeloblast is the predominant cell in the peripheral blood and bone marrow promyelocytes myelocytes, and metamyelocytes are also present

D ACUTE MONOCYTIC LEUKEMIA This disease occurs in adults from the fourth to sixth decades of life The onset is acute, with marked toxicity, and the short clinical course

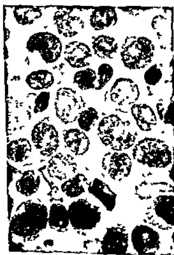


Figure 157 A... The nuclei are irregular ... e cytoplasm

(weeks to several months) continues to be fulminating Sepsis is a prominent feature and extensive infiltration of the gums and skin as well as hemorrhagic manifestations are the rule There is usually minimal lymphadenopathy and splenomegaly A uniform infiltration of monoblasts and monocytes are present in the peripheral blood and bone marrow

The atypical manifestations may be low grade fever bizarre cutaneous lesions arthralgia or migratory thrombophlebitis in addition to the usual leukopenia The picture of the bone marrow is often suggestive but not pathognomonic of the disease There are numerous monocytes histiocytes and reticulum cells These clinical and hematologic findings may often simulate those of chronic infections various granulomas or collagen diseases

E ACUTE STEM CELL LEUKEMIA This type of leukemia constitutes a morphologic entity rather than a distinct clinical picture The predominant cell is an undifferentiated blast



Figure 158 Stem cell (undifferentiated) leukemia (bone marrow) Very primitive cells which are difficult to classify as to type (Oil immersion)

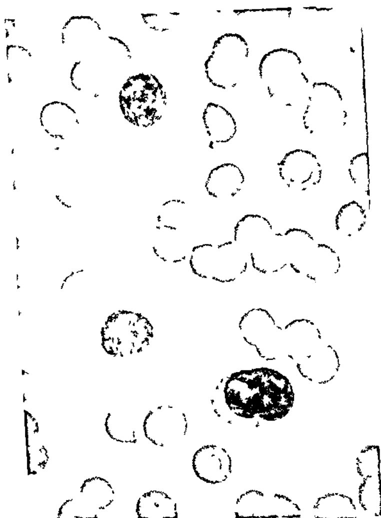


Figure 159 Plasmacytic leukemia (peripheral blood) Eccentric dense nuclei with clear area (hof) in cytoplasm near nuclei Both mature and immature forms are present, the latter are the larger cells with indistinct nucleoli (Oil immersion)

cell having none of the features which characterize the myeloblast, lymphoblast, or monoblast However differentiation into one of the recognized types of acute leukemia often occurs after a variable period of time

F PLASMACYTIC LEUKEMIA Primitive plasma cells occasionally appear in the peripheral blood of patients who have multiple myeloma Examination may disclose typical lesions demonstrable on roentgenograms, Bence Jones proteinuria, or changes in the serum globulin The cells are occasionally so primitive and atypical that they resemble the lymphocytes which are present in the leukemic phase of a lymphosarcoma

G ERYTHROLEUKEMIA This is a rare type of acute leukemia which usually occurs in adults The onset may be acute or insidious and the course of the disease is moderately progressive (three to six months) The clinical course is like that of acute or subacute granulocytic leukemia and is probably a developmental stage of these types of leukemia The bone marrow and peripheral blood present a mixture of primitive



Figure 160 Plasmacytic leukemia (Peripheral blood Oil immersion)

red blood cells (which may have a megaloblastoid appear ance) and immature granulocytes This condition is frequent ly mistaken for some type of hemolytic anemia because of the increased numbers of erythroblasts

III Chronic Leukemia (Table IV)

A CHRONIC GRANULOCYTIC LEUKEMIA This type of chronic leukemia may occur at any age but is rarely present in child hood The initial symptoms are weakness fatigue or aware ness of a mass" in the upper left quadrant of the abdomen This disease is frequently disclosed when routine examination reveals leukocytosis mild anemia or marked splenomegaly As a rule these patients are not acutely ill at the onset of the disease However the symptoms become severe in the final stage of the disease or when there is a conversion to acute leukemia The blood picture reveals an orderly pro

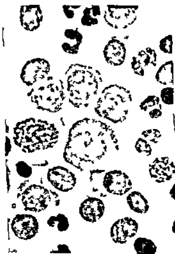




Figure 161 Erythroleukemia (Bone marrow Oil immersion)

Figure 162 Erythroleukemia (bone marrow) Note primitive granulocytic and erythropoietic cells the latter showing thicker cytoplasm and very dense chromatin in nuclei (Oil immersion)

gression of all phases of granulopoiesis from the myeloblast to the neutrophil, as well as an increase in the number of platelets The bone marrow examination discloses marked proliferation of all forms of granulopoiesis including the neutrophilic, eosinophilic, and basophilic series The number of megakaryocytes is markedly increased, as indicated by the thrombocytosis which is usually present There is often a tendency to bruising despite the great increase of blood platelets This has been ascribed to a qualitative defect in the platelets (thrombasthenia), or to defective thromboplastin formation

There may be an unusual variety of clinical pictures in the atypical forms of chronic granulocytic leukemia The initial manifestation may be a long standing asymptomatic leukocytosis which leads to a search for the source of chronic infection An initial erroneous diagnosis of polycythemia vera may be made when erythrocytosis and thrombocytosis, with somewhat elevated hematocrit values, are present In these cases,

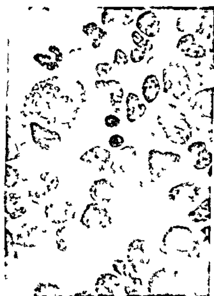


Figure 163 Chronic granulocytic leukemia (bone marrow) Marked augmentation of granulocytic cells in all phases of maturity (Oil immersion)

the splenomegaly may occur either early in the disease or at a later stage In rare cases the patient may present a typical myelofibrosis which subsequently progresses to granulocytic leukemia

Polycythemia vera may be confused with this type of chronic leukemia especially when there is a significant leukocytosis Other conditions mistaken for chronic granulocytic leukemia include infections severe bleeding or replacement of the bone marrow by carcinoma or lymphoma which often exhibit immature granulocytes in the peripheral blood (leukemoid reaction)

B CHRONIC LYMPHOCYTIC LEUKEMIA This type of leukemia usually occurs in adults The initial manifestation is generally a diffuse symmetrical asymptomatic lymphadenopathy, with no systemic symptoms There may be a mild splenomegaly and palpable "masses" in the abdomen The diagnosis of this disease is freq ently made when routine hematologic exami

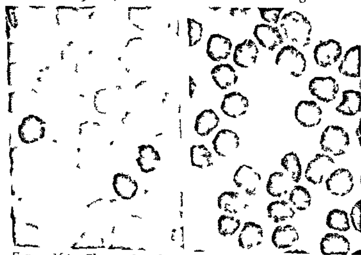


Figure 164 Chronic lymphocytic leukemia (peripheral blood) Small dense cells with scanty dark cytoplasm and very dense clumped nuclear structure (Oil immersion)

Figure 165 Bone marrow from patient figure 164

gression of all phases of granulopoiesis from the myeloblast to the neutrophil as well as an increase in the number of platelets The bone marrow examination discloses marked proliferation of all forms of granulopoiesis including the neutrophilic eosinophilic and basophilic series The number of megakaryocytes is markedly increased as indicated by the thrombocytosis which is usually present There is often a tendency to bruising despite the great increase of blood platelets This has been ascribed to a qualitative defect in the platelets (thrombasthenia) or to defective thromboplastin formation

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Figure 163 Chronic granulocytic leukemia (bone marrow) Marked augmentation of granulocytic cells in all phases of maturity (Oil immersion)

CHRONIC LEUKEMIA

Duration	*Distinguishing Clinical Features*	*Atypical Characteristics*	*Differential Diagnosis*
2 to 5 years	Marked splenomegaly No lymphadenopathy Mild anemia Thrombocytosis	Longstanding asymptomatic leukocytosis Splenomegaly	Myelofibrosis Polycythemia rubra vera Severe infection or bleeding Carcinoma or lymphoma (a) replacement (b) leukemoid reaction
3 to 20 years	Symmetrical generalized lymphadenopathy Mild splenomegaly No systemic manifestations until late in course of disease Hypersplenism and thrombopenia auto immune hemolysis	Leukopenia No lymphadenopathy No splenomegaly Unexplained anemia or thrombopenia	Lymphocytosis in aged persons Chronic infections Granulomas Response to neoplasm collagen diseases Leukemic lymphosarcoma
1 to 3 years	Hepatosplenomegaly Pancytopenia Cutaneous infiltration Marked monocytosis and histiocytosis	[illegible]	[illegible] Pre-leukemic state or early leukemia Atypical lymphoma
3 to 12 months	Severe systemic manifestations Asymmetrical lymphadenopathy	Acute sepsis Prolonged viral type infection Acquired hemolysis	Chronic lymphocytic leukemia Infectious mononucleosis

TABLE IV

Type of Leukemia	*Cytology*	*Age Group*	*Onset*	*Clinical Course*
Chronic Granulocytic	Proliferation of all forms and stages of granulopoiesis	All ages Rare in childhood	Insidious	Chronic May convert to acute leukemia
Chronic Lymphocytic	Mature lymphocytes Dark blue cytoplasm heavily staining nuclei	Older persons	Asymptomatic for period of years	Progresses slowly
Chronic Monocytic	Monocytosis Reticulum cells Fine reticulated nucleus blue nucleoli thin grey blue cytoplasm	Older persons	Chronic	Progressive. May develop into acute leukemia
Lymphosarcoma (Leukemic Phase)	Abnormal lymphoid cells Spindle shaped nucleus ragged cytoplasm bilobed or indented nuclei	All ages	Stormy or insidious	Rapid progression

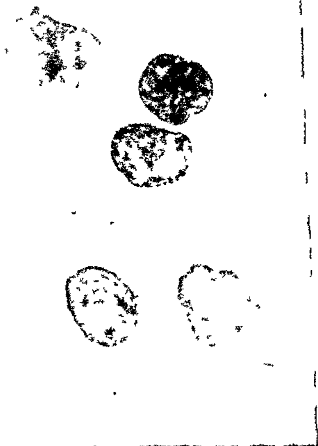


Figure 166 Lymphosarcoma leukemic phase (peripheral blood) Large bizarre lymphocytic cells with dense chromatin structure in nuclei which may be indented or kidney shaped There are several smudge cells They resemble atypical lymphocytes present in infectious mononucleosis (Oil immersion)

nations are done for unrelated conditions In some cases the lymphadenopathy is painful due to pressure on the adjacent structures or may cause disfigurement Herpes zoster occurs frequently in this type of leukemia As the disease progresses fever night sweats loss of weight anemia and thrombocytopenia may occur There is usually a significant leukocytosis with a high percentage of mature lymphocytes in both the peripheral blood and the bone marrow

Leukopenia together with anemia and occasionally thrombopenia may be the presenting hematologic findings Splenomegaly and lymphadenopathy are not marked when these hematologic features are present Under these circumstances it may be extremely difficult to establish the diagnosis of chronic lymphocytic leukemia This is due to the fact that a number of other conditions may be simulated particularly leukemic lymphosarcoma and replacement of the bone marrow by neoplasm

The differential diagnosis would also include lymphocytosis occurring in elderly persons chronic infections (especially tuberculosis and other granulomata) response to the lymphomas without specific infiltration of the bone marrow and advanced stages of carcinoma The bone marrow pictures of patients having lupus erythematosus or rheumatoid arthritis have also been mistaken for chronic lymphocytic leukemia

C Leukemic Phase of Lymphosarcoma This condition may occur at any age and is associated with more profound systemic manifestations than those present in chronic lymphocytic leukemia There is an asymmetrical lymphadenopathy in this condition The differentiation between leukemic lymphosarcoma and chronic lymphocytic leukemia may be extremely difficult since mature forms of lymphocytes are common cytologic features The diagnosis of lymphosarcoma may be readily established when the lymphoid cells have indented bilobed or spindle shaped nuclei a blue cytoplasm having a ragged outline and are pleomorphic These abnormal cells which simulate tissue cells transplanted in the blood stream are also present in the bone marrow Aspiration of this mar

"atypical" acute leukemias to be the rather insidious clinical course which occurs despite the apparently acute process found on cytologic study Although these features may be only of academic interest at this time, they may prove to be of value when more effective therapeutic measures are available

V. Technics

1. Preparation of the Slides. These illustrations depict the technic which is used in our laboratory for preparing a blood film The proper amount of blood is placed on a clean slide which is held in a horizontal position Another slide is then placed vertical to the drop of blood and allowed to spread The surfaces of the slides are gently approximated and the vertical slide then spreads the blood in a gentle, smooth, and even manner When the proper technic is used, and the vertical slide is not pushed or pulled excessively, this procedure results in an even distribution of the blood We have found the best method for cleaning slides is to store them in methyl alcohol, wash in hot water and then carefully dry them with a "lint free" cloth before using

The bone marrow is also spread on slides in the same man-

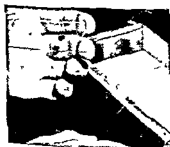




Figure 167 Proper amount of blood on slide before smearing (Preparation of peripheral blood film and bone marrow slide Figures 167, 168, 169, 170)

Figure 168 Position for holding two slides when spreading blood across edge of vertical slide

row is often difficult due to its fibrotic quality This condition is frequently confused with acute monocytic or lymphocytic leukemia, when the cells have a more 'blastic" appearance (See Table III)

D CHRONIC MONOCYTIC LEUKEMIA (RETICULOENDOTHELIOSIS) This is a rare chronic condition which occurs in elderly persons The characteristic symptoms are usually weakness, fatigue, the pallor of anemia, a slight bleeding tendency which is associated with thrombopenia, and leukopenia A moderate splenomegaly and infiltrated cutaneous lesions are usually present There may be some monocytosis in the peripheral blood, and primitive monocytes and reticulum cells are occasionally present Frequently, however, no primitive cells are apparent and the only indication of bone marrow replacement is the paucity of white blood cells and platelets On the other hand the bone marrow may show a moderate to marked infiltration of reticulum cells, monocytes, and histiocytes, in various stages of maturity The histologic picture of the cutaneous lesions reveals very primitive reticulum cells

It is extremely difficult to substantiate the diagnosis of this disease, since the majority of cases eventually progress to some type of acute leukemia The remarkable response of the reticuloendothelial system, associated with chronic sepsis or neoplasia, has also been confused with this disease process

IV. Summary

We have attempted to describe the clinical and laboratory differentiation of leukemia The typical forms of acute and chronic leukemia can usually be readily identified by the clinical findings and the characteristic hematologic picture However, of more importance are the diagnosis and differentiation of the "atypical' forms and the "preleukemic" state These types of the disease may masquerade as other syndromes, especially hypersplenism, granuloma, or chronic infections, and may progress over a long period of time before they are recognized as some type of acute or chronic *leukemia* We have also noted the most important feature of the

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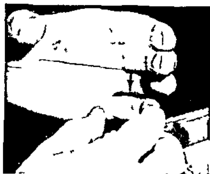
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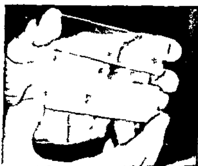


Figure 169 The blood is smeared evenly on horizontal slide without pulling or pushing of vertical slide

Figure 170 Completed slides of peripheral blood and bone marrow

ner to procure an even distribution of the spicules on the slide

2. ***Staining Technic.***

A PERIPHERAL BLOOD A good quality of Wright stain (preferably one which has been stored to allow "aging") is used Although the time for staining varies with each quantity of stain, the average is two or three minutes for Wright stain followed by dilution with buffered distilled water (eight or 10 drops) for eight to 10 minutes In peripheral blood films the morphology and toxicity of the granulocytes, as well as changes in the erythrocytes and platelets, are readily determined with this staining technic

B BONE MARROW We prefer the May Grunwald Giemsa staining technic The May Grunwald stain is applied in a concentrated form for two minutes followed by dilution with buffered distilled water (eight to 10 drops) for four minutes The slides are then washed with distilled water to remove the excess diluent The Giemsa stain is freshly prepared (90 drops of concentrated dye to one ounce of buffered distilled water is sufficient for approximately 16 slides) and applied to the slides for 15 minutes A properly stained bone marrow will disclose vividly clear colors in all the cells We have found this stain to be far superior to Wright stain for staining bone marrow slides

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